THE MECHANICS OF THE DIGESTIVE TRACT

"I am convinced that it is by frequent interchange of opinion between the physiologist and the physician that the common goal of physiological science and of medical art will be most quickly and safely reached."—IVAN P. PAVLOFF

"I hav finally kum tu the konklusion that a good reliable sett ov bowels iz wurth more tu a man than enny quantity ov brains"—JOSH BILLINGS

THE MECHANICS OF THE DIGESTIVE TRACT

AN INTRODUCTION TO GASTROENTEROLOGY

BY

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WITH ONE HUNDRED ILLUSTRATIONS

SECOND EDITION

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THESE PAGES ARE
AFFECTIONATELY DEDICATED
TO
MY FATHER AND MOTHER

PREFACE TO SECOND EDITION

This is practically a new book in plan and scope. The first edition was little more than a detailed statement of the gradient theory with its bearing on the problems of gastroenterology; this one represents a determined effort to make readily available to thoughtful practitioners such information about the mechanics of the digestive tract as they need daily in their struggles to improve their diagnostic and therapeutic technic.

I have an idea that gastroenterology is some day going to forge ahead spectacularly much as cardiology did at the beginning of this century. Those who were students of medicine in 1900 will remember that a heartbeat then was a heartbeat, and little more could be said about it; murmurs were the phenomena to be studied. Then a few progressive men turned up the long-forgotten papers of Gaskell and His; they saw the tremendous bearing that these highly technical contributions might have on clinical problems, and soon everything was changed. Now the heart specialist is more interested in disturbances of conduction than he is in murmurs, and daily he recognizes and treats a score of important conditions for which until recently he had not even a name.

Are we in gastroenterology any more awake today than were the cardiologists in 1900, that is, better prepared to recognize promptly the importance of epoch-making papers published in journals devoted to physiology and anatomy? I hope we are, and I think it augurs well for the future that more and more books are now appearing in which the results of research in special fields are so well epitomized and reviewed as to make them readily available for use by practitioners of medicine.

It may be of interest to note that in the five years since the appearance of the first edition of this work the idea of a gradient of activity down the intestine has received considerable support from workers in various parts of the world, and a number of my early observations have been confirmed.

The whole gradient idea has been strengthened by the work of Murray, who has shown that even in tissue cultures, muscle cells from the embryonic auricle will beat many times faster than will those from the ventricle. This must mean, as Dr. Child and I have always felt, that the gradients are not due purely to functional adaptation during life, but that they are basic, and built into the very structure and chemical composition of the individual cells.

The bibliography of the present volume, containing 900 titles, is probably the best part of the book. The papers referred to have all been read or looked over by me, and their messages incorporated in the text. I know that I must have missed or forgotten many good articles, but the literature is now so enormous that even a fast reader can hardly keep up with it; and from those whose good work I have slighted I can only beg forgiveness, and a reprint.

Some may perhaps doubt the propriety of publishing, as I have done here, the likenesses of living contributors to the subject under discussion; but I could see no valid reason why the readers of this book should not share the pleasure and inspiration that is mine each day as I glance at the gallery that adorns the walls of my laboratory. It does us good to know those who have taught us much, and we are the better for having literally and figuratively looked up to them.

It is a pleasure to acknowledge here my indebtedness to my wife for her help with the proof sheets, to my colleagues, Drs. Balfour, Eusterman, Mann, McVicar, and Vinson, who were kind enough to read some of the chapters in manuscript and to make helpful suggestions and criticisms, and to my friend, Paul Hoeber, for his faith in me and my work. I feel also that I cannot close this book without making some acknowledgment of the great debt I owe to the men who have so generously dedicated to research medicine all the profits of a great institution, and have thereby set free from routine tasks a group of men who, like myself, love to study and experiment. If I had gone on carrying the burden of private practice it is doubtful if I would ever have had the courage to start on this edition, or the time and strength to finish it.

Walter C. Alvarez.

Rochester, Minn.

November, 1927.

PREFACE TO FIRST EDITION

In 1913, while doing some work on the absorption of gases injected into loops of intestine, I noticed differences in irritability in different parts of the bowel; that is, the jejunum reacted actively to distention, while the ileum generally responded but little. It promptly occurred to me that this graded difference in irritability might account for the downward progress of food in the bowel, because it seemed reasonable to suppose that material would have to move from the more irritable and active regions to the less irritable and active ones. While attempting to show these differences in irritability with excised segments of intestine, I found that the rate of rhythmic contraction of the muscle is graded downward from the pylorus to the ileocecal sphincter. Remembering how much the heart specialist has profited by the careful study of conduction along a similar rhythmic gradient from the sinus node to the ventricle, I was filled with the hope that a careful analysis of the gradient found in the bowel might throw light on the mechanism of peristalsis and might put more system into the science of gastroenterology.

As time goes on that hope seems more and more likely to be realized. During 1915, gradients of rhythmicity, irritability and latent period were found in the stomach; and a sort of pacemaker was located on the lesser curvature near the cardia. Later, my assistants and I showed that in addition to the rhythmic gradients in the stomach and intestine, and probably underlying them, there are gradients in metabolism. Ways were found in which these chemical gradients can theoretically be upset; and actually they were found upset in many of the sickly or distempered animals studied. While this laboratory work was going forward a careful review was made of our knowledge of peristalsis both in health and disease; and it was found that the idea of a

gradient of forces which can be flattened or reversed offers the best, the simplest, and often the only explanation for many of the phenomena observed by the physiologist, the internist, the roentgenologist and the surgeon.

In 1920, at the kind invitation of Dr. J. T. Case, then President of the American Roentgen Ray Society, I prepared a short summary of my views which was presented before the Society's meeting in Minneapolis as the First Caldwell Lecture. This little book has developed as an elaboration and amplification of that lecture. I only hope it will be a help and convenience to those practitioners and roentgenologists who are already finding the gradient theory useful in their work, and who wish to know more about the subject. I have tried to make it sufficiently technical for the research worker in physiology and yet sufficiently readable and practical for the medical student or the physician who is looking for help on a clinical or surgical problem. Such students and practitioners will find summed up in Chapters IV, VIII, IX, X and XI[1] most of the data essential to an understanding of the mechanics of digestion; and with the help of the extensive bibliography and the paragraphs at the end of Chapter XII,[2] they can easily gain access to everything else of value which has been written on the subject. I think the chapter on technic will be helpful to research workers, because the information embodied in it has hitherto been scattered through many articles in different languages.

Although many of the observations upon which the idea rests have been verified repeatedly, and although, as Wallace says, "there is no more convincing proof of the truth of a comprehensive theory than its power of absorbing and finding a place for new facts, and its capability of interpreting phenomena which had been previously looked upon as unaccountable anomalies," I must, in all fairness to my readers, emphasize the fact that much of what is written in Chapters IX and X[3] is purely suggestive. Thus we can easily show that there is a rhythmic gradient down the intestine; we can show that the gradient is upset in a distempered

[1] In Ed. 2, corresponding Chapters are XVIII, XII, XXIV and XXV.

[2] In Ed. 2, Chapter XXVII.

[3] In Ed. 2, Chapters XXIV and XXV.

dog; and we can show with excised segments *in vitro* how easy it is to reverse a normal gradient by adding certain poisons like KCN to the Locke's solution. We can speak positively about those things, but we must be careful when we come to say that the reversal found in the sick dog is responsible for the refusal of that dog to eat, and for the inability of his stomach to pass onward the food which has been forced upon him. The observations are highly suggestive; the theory based upon them is proving very useful in explaining the phenomena of indigestion, but we must not lose sight of the fact that it is a theory; that it has weak places, and that much work must yet be done upon it.

As such work will undoubtedly modify or invalidate some of the interpretations which seem logical at this time, it would certainly have been safer and perhaps better if I had left out much of the theorizing which now enters into this little book. By so doing I could undoubtedly have saved myself from future regrets and criticism. I feel, however, with Darwin, that "without speculation there is no good (or) original observation," and that "the observer can generalize his observations incomparably better than any one else." In other words, it would seem that one who has wrestled with a problem day and night for many years, and who has collected all sorts of data bearing upon it, should be most fitted to theorize, to suggest, and to point out the possible applications of his work. He can furnish the greatest number of jumping-off places for further research; and even those who are incited to prove him wrong may thereby advance the field of knowledge. The only danger is that he and some of his less critical readers may come to regard the suggestions and theories not as a scaffolding for the building of an edifice but as a substantial and finished structure. In this connection a writer may have more to fear from his enthusiastic friends and disciples than from his enemies.

Another danger at this time is that some of the building blocks taken from other edifices to be used now as foundation stones may not bear the strain. I think it was Darwin who said that a theory builder ought really to write to many of

the men whom he quotes to see whether they still hold firmly to their published opinions, and whether they approve of the interpretations which he is placing upon their work.[1] It is even better when he can repeat many of the more important and crucial experiments in his own laboratory; and more of that I hope to do in the future. For the present, I can only say that few statements have been made in this book which are not based either upon my own observations or upon a careful reading of several original articles.

I wish gratefully to acknowledge my indebtedness to Dr. Walter B. Cannon who helped me to get started on these problems; to Dr. Saxton T. Pope who aided me with my first little laboratory in San Francisco; to Dr. George H. Whipple, Director of the Hooper Foundation, whose assistance and wise counsel have helped me over many a difficulty; and to Miss Esther Starkweather, Dr. Fletcher B. Taylor and Miss Lucille Mahoney, who have assisted me faithfully with many of the experiments.

WALTER C. ALVAREZ.

SAN FRANCISCO,
Sept. 1, 1921.

[1] Since writing this I have found that it was Huxley who said: "The great danger which besets all men of large speculative faculty is the temptation to deal with the accepted statements of facts in natural science, as if they were not only correct, but exhaustive; as if they might be dealt with deductively, in the same way as propositions in Euclid may be dealt with. In reality, every such statement, however true it may be, is true only relatively to the means of observation and the point of view of those who have enunciated it. So far it may be depended upon. But whether it will bear every speculative conclusion that may be logically deduced from it is quite another question." The Life and Letters of Charles Darwin. N. Y., 1897, p. 315.

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CHAPTER I

THE AUTONOMY OF THE DIGESTIVE TRACT

The human mind is not ready to look for new explanations for well-known phenomena, or even to accept them when found, until its contentment with the old explanations has been disturbed. Whenever I describe some of the regional differences in behavior which can easily be demonstrated in the excised stomach and bowel, someone is almost sure to say: "Oh, that is due to the autonomic and the sympathetic." Another says it is a "reflex." So far as they are concerned the matter is settled, so why waste more time on it! When I point out that the peculiarities persist in little pieces of muscle which have been cut out and kept in the ice box for a few days, these individuals take refuge in the fact that there are ganglion cells in Auerbach's plexus.

Now the most paralyzing thing in scientific work is a facile explanation which puts a stop to further curiosity without really advancing our knowledge of the subject, and I have never been able to see the value of pushing the explanation for a mechanical phenomenon out of the organ in which it might be studied, and into a tiny ganglion where it can hardly be followed. It seems to me that many even of the teachers of physiology have a wrong idea of the nervous system and its relation to the viscera. They look at it somewhat as an electrical power house which not only controls the activities, let us say, of the various trains running over a railroad, but supplies the motive force. My analysis of the literature makes me feel that we should look at it more as a telephone switchboard with wires which carry messages

of warning and advice from one engineer to another. The trains supply their own power, and the differences in speed and other activities are due to peculiarities in the structure of the engines, peculiarities in fuel, differences in the gradient of the road, etc.

EVOLUTION OF THE NERVOUS SYSTEM

This idea comes out more clearly as we study the development of the nervous system in lower forms of life. First, we have the unicellular organisms which naturally have no difficulty with conduction and do not need nerves. Next, perhaps, come the sponges with muscles but still no nerves. These muscles respond to direct mechanical stimulation transmitted through the overlying epithelium. There is a little conduction from muscle cell to muscle cell, but it is so slow and its spread is so limited that there is no coordination between the movements of adjacent fingers of the sponge (Parker, 1919). Next in the scale of development come the animals with nerve nets interposed between the epithelium and the muscles. Such a nerve net in the sea anemone enables the animal, when touched, to contract all over at one time. The stimulus spreads out through the net somewhat as ripples spread from a stone thrown into a pond. If the impulse is slight, only a few muscles will respond locally; but if the impulse is strong, every muscle in the animal will contract (Bethe, 1903). A little higher in the scale we find nerve nets which are "polarized," that is, they conduct better in one direction than in another (Parker, 1919, p. 130). We shall see later that Auerbach's plexus is probably to a considerable extent, "polarized." The trouble with this type of nervous system is that it is uncentralized. There is no single organ to which experiences can be referred or from which volitional impulses can emanate. Moreover, a stimulus at one point is likely to spread all over. These difficulties are overcome in the higher animals by the breaking up of the conducting paths into three relays, consisting of a sensory, a connector, and a motor neurone. The connections between these neurones are so made that impulses can

pass in one direction only. Furthermore, by means of association fibers, impulses may travel to smaller or larger groups of muscles where they will bring about coordinated movements. The higher the animal is in the scale of existence, the more complicated and more numerous become these association fibers with their valvelike synapses (Parker, 1918[b]).

THE FUNCTION OF THE NERVES IS TO EXPEDITE CONDUCTION

It must not be forgotten, however, that in the more complex animals, alongside of the highest type of synaptic system, we find not only the primitive nerve nets, as in the bladder, arteries, and perhaps intestine, but we find evidence of the original protoplasmic transmission from cell to cell. Similarly, in a modern city, we find, alongside of the telephone, the original messenger boy. The thing to be kept in mind is that the nervous system in all its stages of development has one big function, and that is to expedite conduction. Loeb (1900) has shown by numberless experiments that there is no storage of wisdom in ganglia and "centers." He takes up one complicated reflex after another, "purposeful reactions" and "instincts," and shows that they are due simply to localized peculiarities of structure and chemical affinity.

All sorts of properties have been ascribed to the ganglion cells, but it appears now that these structures serve more as nutritional centers for the nerve fibers than as storehouses of wisdom and tone. Bethe (1898, p. 403) was able by microdissection to trim off all such cells from the nerve bundle going to one of the antennae of a small crayfish, and found no difference in the tone and reflex irritability of the muscles in that antenna. This suggests strongly that the reflex impulses do not even have to pass through the ganglia, much less originate in them. Similarly, if we remove the central ganglion from an ascidian, its complicated reflexes are still carried out. The only difference is that they need a stronger stimulus and they are executed more slowly because conduction is then effected through the nerve net (Loeb, 1900, p.

35; Jordan, 1908). Most of us think of the pupillary response to light purely as a complicated brain reflex, but it has been shown that not only does the pupil of the excised eye react, but small muscle bundles cut out from the iris will respond directly to the stimulus of a strong light (Parker, 1919, p. 51). Even more remarkable is the fact that a beheaded shark can swim as if there were little the matter with him, and a frog can catch flies, swallow and digest them for weeks after his forebrain has been removed.

I cannot imagine any one arguing that the ganglia and nerves are useless simply because they can be so well dispensed with in an emergency. One might as well argue that the telephone is useless because a factory can keep at work after a fire has destroyed its automatic switchboard. I may seem to belittle the importance of that switchboard, but it is only to divert the minds of some from the idea that it is the guiding brain of the factory and the force that makes it work.

The factory is ordinarily not autonomous, because the workers must have a central office through which they can keep in touch with the selling and buying world, but it is facultatively autonomous in the sense that it can keep going for some time even if its lines of communication are broken. Each machine or department of the factory contains within itself the mechanism required for a particular type of work, and all it needs from the central office is that degree of control that will enable it to coördinate its activities with those of the other machines or departments and with the requirements of the trade.

THE FACULTATIVE AUTONOMY OF THE DIGESTIVE TRACT

Similarly, the digestive tract is doubtless better off for having an extrinsic nerve supply, but many experimenters have shown that it can go on with its work quite well without it (Cannon, 1906[a], Rubaschoff, Pavloff, 1910, Krehl, Katschkovsky, Koennecke). It continues to show good rhythmic activity when removed from the body and supplied with oxygen, and even small segments of bowel or little strips of

the muscular coat will show typical peristaltic activity for days after their excision.

I emphasize these points not because I wish to start a childish controversy over the relative values of different parts of the body, but because I wish to impress students with the need for studying the mechanisms underlying peristalsis right in the bowel itself and not in the celiac ganglia and adjacent nerves.

CHAPTER II

THE MYOGENIC NATURE OF THE RHYTHMIC CONTRACTIONS

In some ways it seems foolish to waste time over this question of myogenic and neurogenic origins because normally the muscle and the nerves work together, and there is no doubt that the nerves serve a useful purpose; but it seems foolish also that in the face of the almost unanimous evidence in favor of the myogenic view, textbook writers should continue to assert unequivocally that the neurogenic one is correct, and should continue to base that statement on a faulty understanding of the work of one man. This behavior on the part of physiologists is probably one of the best examples I could give of the results which follow when men are dominated by a mental bias in favor of neurogenic mechanisms. As I have said in the preceding chapter, I protest against that bias, not because I think one in favor of myogenic origins would be any better, but simply because I fear that it is keeping men from getting down to that study of the local mechanisms in the stomach and bowel which I think will eventually be most fruitful.

Work of Magnus. The definite statement is made in most textbooks that the rhythmic contractions of the bowel are neurogenic and that this has been proved by the work of Magnus. Now, on looking up that work one finds a series of six papers. In the first Magnus describes the technic of using excised segments of intestine in Locke's solution, and records a number of preliminary studies. In the second he shows that the longitudinal muscle can be pulled from the circular, carrying with it practically all of Auerbach's plexus. This is due to the fact that the nerve cells lie in grooves and deep recesses in the longitudinal layer. He studied his preparations after careful staining and found that only small fragments of the plexus remained adherent to the circular layer. These little pieces were so widely scattered and so badly damaged that he felt they could be disregarded. As the

longitudinal muscle with the plexus attached contracted rhythmically and the circular did not, he was satisfied that the beat was neurogenic. In his fourth paper, he showed that the active, plexus-containing strips and the quiet denervated ones reacted differently to electric stimuli. Some difficulties were met with in this study which might have caused Magnus to doubt the sureness of his ground, but his troubles began when he started studying the effects of drugs on the segments. He was delighted at first to find that some of the drugs brought out distinct differences in the behavior of the plexus-free and plexus-containing segments, but later he discovered that others such as barium chloride, strophanthin and pilocarpin would produce rhythmic contractions even in the denervated segments. This led him to the conclusion that, although the preparations of circular muscle which he had been using were denervated sufficiently for most types of physiologic study, they were not denervated sufficiently for pharmacologic work. In order to remove all traces of the plexus, he seared the outer surface of the circular muscle with nitrate of silver; and when strips treated in this way failed to contract rhythmically even in the presence of the above-mentioned drugs, he felt sure that he had gotten rid of all traces of the plexus.

Unfortunately for his peace of mind, Magnus found next that physostigmin would bring out beautifully rhythmic contractions even in the partly charred strips which he was sure were plexus-free. These contractions are shown in Figure 1, A, copied from his paper. As he could go no further in the matter of denervation, and as physostigmin brought out rhythmic contractions in strips which reacted in a typically "denervated" way to other tests, Magnus had to admit that the contractions could be myogenic. He found, moreover, that physostigmin acts in the same way on the denervated muscles of the marine worm, *Sipunculus nudus*. In that animal he had no doubt about the completeness of the denervation because the ventral nerve cord is easily visible and can be dissected off in its entirety.

In 1914 Gunn and Underhill repeated this work of Magnus, using a better technic. They felt that they could cut down the

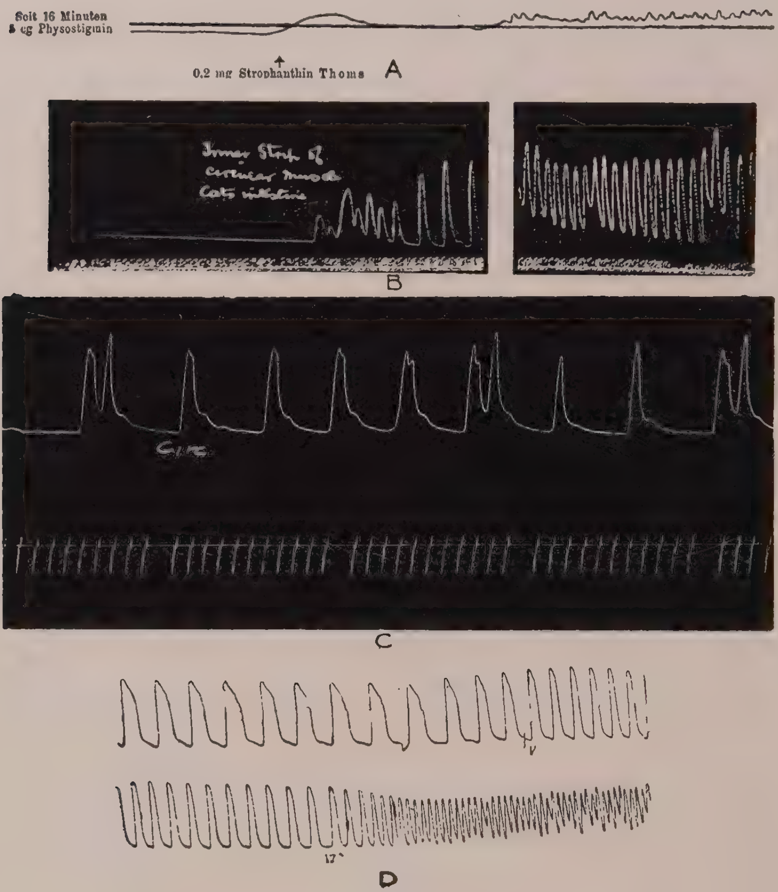

FIG. 1.

(*A*) Plexus-free preparation contracting rhythmically. (*From Magnus.*)
(*B*) Denervated muscle. (*From Gunn and Underhill.*)
(*C*) Tracing from one of my own experiments with denervated muscle.
(*D*) Rhythmic changes in the evolution of hydrogen when acids act on chromium. Note increase of rate with rise in temperature of the solution. (*From Ostwald.*)

severity of the shock of dissection by tearing the strips apart under iced Locke's solution, which would act as an anesthetic. As they had good reasons for believing that the silver nitrate used by Magnus in searing the outer surface of the circular layer would diffuse into the tissue and damage the muscle throughout the strip, they avoided using it by taking for their experiments only a few fibers from the inner side of the ring. In this way they obtained muscle which would

FIG. 2. R. Magnus.

seem to have been plexus-free, and which contracted rhythmically without the help of drugs (Fig. 1B, copied from their article).

This work was repeated by Miss Mahoney and me (1922[b]) and by Evans and Underhill with the same results. Miss Mahoney and I used fibers taken from the inner surface of the circular layer of muscle from segments of a dog's small bowel which had been left in the ice box for twenty-four hours. Although no ganglion cells were found in the many sections studied under the microscope, these fibers contracted rhythmically. The need for patience in such experi-

ments is shown by the fact that in some cases we had to wait six or seven hours before the contractions began.

Strange to say, strong rhythmic action currents could be detected in segments of intestine which seemed to be perfectly quiet. This suggests that rhythmic chemical processes are constantly going on in the muscle: processes which can give rise to the mechanical contractions. The presence of a little barium or physostigmin seems to act like a clutch between an idling engine and its related machinery.

Tiegs feels that such experiments are still inconclusive because some of the nerve fibers which run from Auerbach's plexus out through the muscle will almost certainly remain. Although it is conceivable that such scraps of nervous tissue without ganglionic connections might give off rhythmic stimuli it does not seem probable, especially when one takes into account the observations recorded in the next paragraph. Tiegs believes also that there may be some small ganglia in the walls of blood vessels, but one would hardly expect them to be supplying rhythmic stimuli to the intestinal muscle.

Resistance to Anoxemia. Almost all of those who have worked with excised segments of bowel have commented on the fact that these bits of muscle may contract more regularly on the second or third day than on the day of removal from the body. They usually maintain their power of rhythmic contraction for five days, but some observations by Mines (1910) suggest that if strips of muscle were to be removed and kept under a septic condition they would live much longer. Now, it is well known that nerve cells do not long survive the stoppage of the circulation, and there is some evidence that sympathetic ganglia are even more vulnerable to anoxemia than are those in the central nervous system (Langendorff, Langley). Furthermore, Cannon and Burket have shown that if parts of the intestine or stomach are compressed and rendered anemic for three and a half hours or longer, practically all the nerve cells degenerate. Hence it does not seem probable that the function of the intestinal ganglia could actually *improve* after forty-eight hours of anoxemia.

It is interesting also that the ability of the muscle to contract rhythmically, its ability to respond to drugs like atropin, pilocarpin, and epinephrin, which are supposed to act on nerve endings, and its ability to respond to barium chloride, which is supposed to act on muscle, are all lost together about the fifth day when the tissue apparently dies. There is no evidence to show that nerves die on one day and muscle on another. One might argue from this that the nerves maintain their function for five days, but I doubt if the drugs are as selective in their actions as we commonly assume. Atropin, pilocarpin, and cocain definitely affect the behavior of unicellular organisms, and the theory of nerve-endings, when closely examined, is found to be a maze of contradictions. Hence it is that we should be slow to accept conclusions drawn, as are those in the next paragraph, from the assumed effects of drugs.

Pharmacologic Proof. Oddly enough, many of the writers who quote the work of Magnus to prove the neurogenic theory of the rhythmic contractions quote that of Bayliss and Starling to prove the same origin for the peristaltic waves. The last-named workers found that when they applied cocain to the bowel or injected nicotin, coordinated peristalsis disappeared but at the same time the rhythmic movements were made more regular and ample. It would seem obvious that if one interprets these experiments to mean that the nerves were paralyzed and that peristalsis is dependent on them, one must accept them also as showing the myogenic origin of the rhythmic contractions.

This work of Bayliss and Starling has been confirmed by Trendelenburg (1917[a], p. 97) and by Thomas and Kuntz (1926[a]) who have injected as much as 2 or 3 gm. of nicotin for each kilogram of body weight. After such doses the bowel usually did not respond to epinephrin or pilocarpin but it contracted rhythmically even more regularly than before the nerves were poisoned. Thomas and Kuntz concluded that their preparations were more thoroughly denervated by the enormous doses of nicotin than they could have been by any process of dissection (p. 606). Similarly, Hammett has shown that excised sengmets of rats' bowel will continue

to contract rhythmically in a 1:4000 solution of cocain, and I have found that segments of rabbits' ileum will beat in a 1:360 solution of novocain or in a saturated watery solution of chloroform or ether.

The only evidence that I can find now in support of the idea of a neurogenic origin of the intestinal contractions is that of Yanase who observed peristalsis in embryo guinea pigs only after the twenty-sixth day when the myenteric plexus and the longitudinal muscle appeared. This, however, is negative evidence and it may be that the muscle was deficient in some other phase of development besides that connected with its nerve supply.

Rhythmic Processes Common in Nature. When one looks about in nature and sees how common rhythmic processes are, it is hard to understand why physiologists should always try to ascribe those in living tissues to the initiative of one particular structure, the nerve cell. Actually one can produce curves closely resembling those traced by a frog's heart by attaching a tambour to a flask in which hydrogen is being developed through the action of hydrochloric acid on chromium. Rhythmic changes take place in the metal which make it alternately resistant and subject to attack by the acid (Fig. 1 D, after Ostwald).

A rhythmic response to a constant force is to be found in the regular dripping of water from a reservoir, and Forbes and Gregg have remarked on several instances of this type of reaction in the body. Quincke produced rhythmic alterations in the shapes of air bubbles trapped under water and placed in the path of a fine stream of alcohol (Loeb, 1900, p. 22). The pulsations of the bubble closely resemble those of a heart, and are due to alterations in the surface tension. Bose has observed rhythmic contractions in the leaflets of plants; and a little higher in the scale, animal tissues are met with which are not typically muscular in structure, but which possess the power of rhythmic contraction. I refer particularly to flagella, cilia (Dellinger, Child), and the tails of spermatozoa. Gray and others have teased out of the mucous membranes of lower animals single cells with cilia

which have continued to lash backward and forward in spite of the absence of any demonstrable nervous tissue.

THE AUTOMATIC RHYTHMICITY OF MUSCLE. The heart beat seems to originate in muscle or muscle-like tissue except in the Limulus, a primitive type of crab; but even in this animal, Garrey has shown that the denervated muscle will contract rhythmically if put into N/2 sodium chloride. Furthermore, Carlson and Meek found that in the embryos there is a stage in which the heart beats although nerves have not yet grown out to it (see also Crozier and Stier). Similar observations have been made by Dekhuyzen on the heart beat in the embryo of the mouse. J. F. Gaskell found that the heart of a leech can be removed entirely from nervous influences without stopping its activity, and the heart of a tunicate will continue to beat when separated from its ganglion and even when removed from the body.

To my mind the most unanswerable argument in favor of myogenic origins is to be found in the fact, observed by many workers, that isolated heart muscle cells which have developed in tissue cultures will beat rhythmically (Lake, Murray and many others). The same thing has been seen also by the Lewises in cultures of smooth and of skeletal muscle. Such findings explain why the heart of the embryo chick can beat after twenty-nine hours of incubation, several days before nerve cells have grown into it.

Other experiments by Loeb (1906), and Nice and Neill have shown that striated muscle and the denervated bells of Medusae will contract rhythmically if placed in the right solutions; in fact, Romanes found that the nerveless centers of some types of jellyfish will beat in ordinary sea water after the shock of the operation has worn off.

It would seem clear from all this that rhythmic contraction must be a property of muscle and muscle-like tissue, and the probability is that it is brought about simply as a result of recurring cycles of chemical activity. That being so, it would seem to me that we should always assume that a rhythmic pulsation has a myogenic origin until, as in the case of the heart of the adult Limulus, we have proof to the contrary. Actually, most physiologists do just the oppo-

site; they assume that the origin is in the nervous system and only reluctantly admit that it might be in the muscle. Naturally, we cannot be absolutely sure of what happens in the intact animal because there the nerves and the muscles always work together, but in forming our opinions on this problem as well as on the many others that confront us in this life we have to be guided by the probabilities. When pulsations die down or cease after a tissue has been bathed in a neurotropic poison, we must suspect that their origin is a predominately nervous one, but when, as in the bowel, the pulsations actually improve in amplitude and regularity, we must lean to the view that their origin is mainly or entirely muscular.

Unfortunately the problem has been somewhat complicated in the last few years by my finding that the same bit of muscle in stomach or bowel not infrequently shows at one time two or three types of local contraction; a slow tonus change, a more rapid, and perhaps fundamental, rhythmic shortening with a rate between five and thirty-five a minute, and a peristaltic contraction. Any theory that is to explain all the facts must throw light on the origins of these three rhythms either in the muscle cells or in the plexus.

CHAPTER III

THE FUNCTION OF AUERBACH'S PLEXUS

Conduction. If the muscle can contract by itself, the next question is: What is Auerbach's plexus good for? The answer is that it undoubtedly serves for the conduction of stimuli and the coordination of movements. A centipede is a colony of legs, each segment of which can walk and attend to its own affairs. Normally they all follow the lead of the head segment. If we cut the nerve cord we get, in effect, two independent centipedes, one of which may want to stand still while the other wants to walk off. The result is that the animal turns from time to time to bite savagely at its rear half which it seems to regard only as a foreign body (Carlson, 1904, p. 286). The hind end of a planarian worm which has grown too long for efficient conduction fails to follow the lead of the front end; it takes firm hold of the aquarium wall, the front end crawls on unconcernedly, and the worm is pulled in two (Child, 1915, p. 131). We would probably have similar conflicts in the bowel, with colic and dynamic ileus as a result, if rapid conduction were not possible through the myenteric plexus and through the nerves in the mesentery. My own measurements indicate that impulses travel about 20 cm. a second through the plexus (Alvarez and Starkweather, 1919). This seems slow for nervous transmission, but it may be that these nets represent early stages in the evolution of conducting tissue, and the rate in the bowel is similar to that observed in the nets of some of the lower organisms (Lillie, 1914, p. 417; Jenkins and Carlson, Hecht, Parker, 1918[a], p. 231).

Preventing Spasmodic Contraction. Still another function of the plexus is probably to keep the muscle from being too active (Bayliss and Starling, 1901, p. 133) or from contracting into a hard knot. It is well known to zoologists that when smooth muscle is cut off from its nervous connections its tone is likely to rise to a point where rhythmic contractions are no longer possible (Magnus, 1904[a], Jordan,

1901, p. 210, Biedermann, 1905). Magnus' difficulty in getting good records from denervated intestinal muscle was due probably in part to the spasmodic contraction which appeared when he removed the plexus. Similarly, Cannon (1906[a], p. 432), when he cut the vagi, sometimes saw a remarkable shrinkage of the stomach into a hard narrow tube. The condition corresponds somewhat to that seen in the spastic paralyses of the voluntary muscles after cerebral hemorrhage.

All these observations have suggested to me the possibility that some of the contraction rings seen in spasmodic ileus, infantile pyloric stenosis, cardiospasm, and Hirschsprung's disease are due not to an excess of nervous stimulation but to an absence of it; and since making this prophecy, a few years ago, I have found an article by Dalla Valle in which he reports his inability to find any trace of nervous tissue in sections from the contracted sigmoids of two brothers who were operated on for megacolon. It is to be hoped now that more such studies will be made by those who are expert in the use of nerve stains. Against my theory is the observation of Wade and Royle (1927) that the obstruction in Hirschprung's disease may, to a considerable extent, be relieved by cutting the lumbar sympathetics on the left side.

Mediating Reflexes. Most physiologists have assumed that Auerbach's plexus must serve as a reflex center for the bowel, but I have always had some doubt about it. In the first place, never having been able to demonstrate Bayliss and Starling's law to my entire satisfaction, I have not felt the need for a synaptic mechanism quite so acutely as do those who accept this reflex as the *sine qua non* of peristalsis; and in the second place, I have been influenced by the testimony of the anatomists, all but one of whom have failed to find the necessary neuronic paths. Some have postulated the existence of axon reflexes, and Kuntz has reported the finding of a few synapses between the processes of cells in neighboring ganglia. Johnson (1918) has since looked for these synapses and has failed to find them, and most neurologists feel that they can hardly be there unless the arrangement of

the neurones in the bowel is quite different from that in the rest of the body.

As will be pointed out in more detail in a later chapter, a reflex arc everywhere else consists of three neurones. The first is afferent or sensory, the second serves as a connector, and the third is efferent, or motor. In the voluntary system the connector fibers are relatively short because they have to run only from one nucleus in the cord or brain to another; but in the involuntary system they are very long because they have to run from the brain and cord out through the vagus and splanchnic nerves to reach the third neurone which, in embryonic life, wandered into Auerbach's plexus (vagus system) or into the celiac ganglia (sympathetic system). As Johnson has shown, after degenerative section of the extrinsic nerves to the bowel, nearly all of Auerbach's plexus disappears, leaving only the local ganglion cells and their processes. Apparently, then, there are but two sets of neurones available in the wall of the bowel; and it is a question whether they are enough for the production of true reflexes.

In accordance with this view is the evidence that Miss Mahoney and I obtained when we failed to detect any abnormality in the reactions of the gut of the heavily strychninized animal which would suggest that synapses had been brought closer together. As is well known, strychnin seems to act principally on the connections between neurones; and Moore and others have suggested that it be used to distinguish between animals with true continuous nerve nets and those with more complicated neuronic systems. (Porter, Moore, Knowlton and Moore, McGuigan and Becht, McGuigan, Keeton and Sloan, and Sherrington, 1911, pp. 42 and 111.) More recently, however, doubt has been thrown on the validity of this technic by the work of Crozier and Pilz, who have found that an organism as complicated as that of the grasshopper does not show the characteristic effect of strychnin.

It must be remembered in all of the discussions about the nature of Auerbach's plexus that none of the staining technics are reliable. Certain fibers show up while others do not, so negative findings are always doubtful, and even the posi-

tive ones may be confusing and subject to different interpretations by different men. One point now seems established, at least for the higher animals, and that is that the myenteric plexuses are not true nerve nets with protoplasmic continuity throughout; although the nerves criss-cross in every direction, they are not fused.

Connecting the Muscle with the Mucous Membrane. There is one group of phenomena which suggests strongly that impulses pass from the mucous membrane, perhaps through Meissner's plexus to Auerbach's and from thence to the muscle, enabling the chemical composition of the food not only to regulate the rate of peristalsis but also to determine the way in which the residues are spread over the absorbing surface, from the duodenum to the lower ileum (Marbaix, p. 271, Jacoby, 1891, London and Sandberg, London and Dobrowolskaja, Babkin, 1925). Thus, in cats, Cannon (1904) found that carbohydrates pass through the small bowel faster than fats, and fats travel faster than proteins; and London and Sivre found that it did not make much difference whether they gave to an animal 50 or 500 c.c. of a particular food: in both cases it was evenly distributed over the bowel, so that all parts of the tube could be put to work.

Suggestive also is the fact observed by Lenz (1923, p. 937) that when the sensitiveness of the mucous membrane of the colon of the cat is dulled by enemas containing local anesthetics, anthraquinon derivatives given by rectum no longer act as purgatives. Somewhat similar observations have been made in the upper duodenum where cocainization of the mucous membrane interferes with the working of the reflex that normally slows the emptying of the stomach. In the stomachs of infants, Rogatz has shown that the tone of the muscular wall varies markedly with the consistency of the food given.

Inflammation of the mucous membrane of the bowel, and particularly of the colon, will sometimes give rise to a telltale puckering of the overlying muscle; and irritation of the same membrane by purges or coarse food will give rise to heightened peristalsis. There is some evidence also that pricks from sharp foreign bodies like pins within the gut will

inhibit the contractions of the overlying muscle so that perforation will be avoided (Exner). The fact that fish-bones and needles can go through the tract without injuring it, does make it look as if some such mechanism must be present, but recent investigations (King and Arnold) have failed to demonstrate it. Only occasionally could King and Arnold influence the tone and activity of the musculature by slight mechanical irritation of the mucous membrane. Vigorous stimulation of the inner coat generally produced relaxation of the bowel which was followed immediately by a strong contraction and an increase in its rhythmic activity. Such sequences of inhibition and contraction are seen so commonly with smooth muscle, and they can be reversed so easily by varying the character or strength of the stimulus, that it seems hardly necessary to drag in a reflex mechanism to account for them.

The fact that Auerbach's plexus is almost certainly of vagal origin, and the fact that in their experiments, stimulation of the vagus rarely affected the muscularis mucosae led King and Arnold to conclude that there is little connection between Auerbach's and Meissner's plexuses. The fact that splanchnic stimulation generally produced relaxation in the outer musculature and contraction in the inner (muscularis mucosae) made them feel also that these nerves must either carry separate fibers for the two coats, or else some of the fibers must divide, sending one branch outward to inhibit and the other inward to stimulate. They thought that their results could be best explained by assuming that Meissner's plexus is a reflex center in connection with the sympathetic fibers, but they realized that they would then have all the anatomists ranged against them. Ranson, who has reviewed this subject from the viewpoint of the histologists, says that "there are no observations which would indicate the presence of sensory cells in the epithelium, sending fibers into the enteric plexuses, such as those which form a characteristic feature of the celenterate nervous system." He admits, however, that on the physiologic side there are many facts that indicate that there must be some type of receptor in the mucosa.

CONCLUSIONS

Actually, we know very little about the functions of these plexuses, but I think we can be sure that their main purpose is to expedite conduction and to correlate the activities of different regions. There are certain simple types of peristalsis in which the help of Auerbach's plexus is probably not required because the excitation spreads from muscle bundle to muscle bundle, and there is little more need for a nervous mechanism than there is in a pond where ripples run out from a splash. In other places, as in the colon of the rabbit, there are many curious types of activity which do not seem to be explainable on the basis either of the myenteric reflex or of gradients of irritability and tone, and there it would seem that there must be a fairly complicated nervous mechanism at work.

I have been impressed also with the way in which, particularly in the digestive tract of the dogfish, stimuli may give rise either to shallow contractions spreading slowly along the muscle fibers, to deep peristaltic waves, to systoles of the whole stomach or bowel, or to strong contractions which do not travel, or which travel a little way and then fade out. Several of these reactions cannot be compared to the ripples in a pond because those follow every splash and they keep going until they fade out or are blocked. In the bowel, therefore, there would appear to be a nervous mechanism, with synapses which can open and close.

Similarly, in the dogfish, I have felt the need for a nervous system with which to explain the way in which, from time to time, the stomach or bowel will suddenly almost double in length. Apparently there is a simultaneous shortening of the circular fibers and a lengthening of the longitudinal ones. I have never seen anything quite like this in the higher animals, but I have seen many systolic types of contraction where it would seem that the impulse must have traveled rapidly either in the plexus or in the mesenteric nerves.

The Anatomy of the Plexuses in the Stomach. A good review of the finer nerve supply of the stomach can be found in an article by Brandt. Within the wall of the organ, the sympa-

thetic fibers seem to run with those derived from the vagi. In some specimens, he found a rich plexus of nerves around the cardia. Along the lesser curvature, he found many nerves and ganglion cells both in the longitudinal muscle and between it and the circular layer. In the rest of the stomach he found ganglion cells only in the longitudinal layer. In the cat he could trace a few fine fibers down into the mucous membrane, but he did not find them in man. The ganglion cells were mainly multipolar and could be divided into three groups: (1) a few minute cells in the submucosa; (2) medium-sized cells throughout the stomach; and (3) large pyramidal cells in the pyloric region. He made the interesting discovery that there is a large bundle of sympathetic fibers running from the left semilunar ganglion to the cardia. Another fine article on the nerve supply of the stomach is by M'Crea.

CHAPTER IV

THE SMOOTH MUSCLE OF THE GASTROINTESTINAL TRACT

I had not been working long on the problems of peristalsis before I became impressed with the need for learning everything possible about smooth muscle. More and more it seemed to me that if I knew just what that tissue would do under certain conditions I could explain many of the activities of the gut. I felt still surer of that when I found how autonomous the muscle is, and how strong its tendency is to contract rhythmically, even in the absence of nervous stimuli. It would seem well, then, in this chapter to enumerate briefly some of the properties and peculiarities of smooth muscle. Although from now on the term *muscle* will often be used, it must not be forgotten that there are nerve cells scattered amongst the contractile fibers, connecting them together and modifying their reactions. To be exact, we should probably use the term *musculoneural apparatus* except in those instances in which we refer to denervated muscle, but the word is long and unwieldy, and after this explanation, I think it will be safe to use the shorter term *muscle*.

Anatomic and Physiologic Characteristics. As is well known, smooth muscle is made up of spindle-shaped cells which vary in size, shape, number of nuclei, etc., in different animals and in different parts of the same animal (Ranvier, p. 433, Pompilian, Lapicque, McGill, Schultz, 1895, Bottazzi and Grünbaum, Paukul, Schiefferdecker). As a rule it contracts more sluggishly than striated muscle does; it takes longer to get started, and it is slower in recovering its original length. Incidentally, the greatest difficulty in working with this type of muscle arises from the fact that one can never be sure what its original length was because of the constant changes in tone. After a number of strong stimuli or sometimes after only one, the muscle may become quite refractory (Parker, 1919, p. 168, Jennings, Woodworth, p. 39), but after

a long rest it seems again to get on a hair trigger so that it will respond powerfully and explosively to a slight stimulus. That is the condition of the digestive tract after the night's rest, and it probably has much to do with the fact that most of us have the daily bowel movement in the morning, immediately after breakfast. With an animal open under salt solution, one can often start a rush wave down the bowel by pinching the duodenum. For some time afterwards, similar pinches will have no effect, but if we wait long enough we will again find the bowel so sensitive that the slightest stimulus will start a wave.

Different Types of Smooth Muscle. Another characteristic of smooth muscle is its ability to maintain a firm and lasting contraction without fatigue. We see this in the muscles which close the shells of bivalves, and we see it in the wall of the colon. It is interesting that the muscle in a bivalve consists of two parts: one which closes the shell and the other which locks it closed. By cutting first one and then the other it can be shown that neither one can do the work of the other (Parnas). Similarly, if a man of average strength tries to hold his arm out perpendicularly to his body he soon finds it a most painful and fatiguing experiment. The deltoid was not designed for such heavy work, but the glutei and back muscles are carrying much heavier loads all day and they do not complain (Sherrington, 1915, p. 191). We learn from this that there are all kinds of muscles, all suited to different purposes. Some, like those in the wings of insects, must contract 300 times a second; others like those in the wings of a hen have little to do. Those who think all muscle is the same forget the differences between the white and dark meats of chicken, between the heart and the gizzard, between tenderloin, round steak and tongue.

I have gone into these differences thus at length because I believe there are similar differences between the muscle in the cardiac and pyloric ends of the stomach (Alvarez, 1916[a,b]; 1917[a,b]); between that in the small intestine and that in the cecum (Alvarez and Starkweather, 1918[b]) and colon (Alvarez, 1918[a]). The muscle on the lesser curvature near the cardia is soft to the touch like coagulated fibrin; that in the pyloric

antrum is tough like gizzard and has a different color. If we stimulate the two with an electric current or with a pinch, we get two entirely different contraction curves; and if we put them into warm oxygenated Locke's solution we get two different types of rhythmic activity. These differences should be expected when we remember that the upper and lower ends of the stomach have different kinds of work to do. The upper end serves largely as a hopper to hold the food; the lower as the mill to do the heavy work. More of these local peculiarities will be described later.

Response to Tension. Another characteristic of smooth muscle in hollow organs is its responsiveness to tension. Most of the motor activities of the stomach and bowel are brought about and regulated largely by the internal pressure due to the presence of food or gas. Cannon (1911,[a] p. 187) has shown that the rhythmic segmentation in the small intestine is due simply to the fact that those muscle fibers which are stretched tend to contract. Their contraction increases the pressure in neighboring segments, and so the process goes on. Cannon has shown also that the waves in the stomach tend to appear at those places where the internal pressure balances the local tone of the muscle. If the pressure is too little or too great there may be no waves (Cannon, 1911[a], p. 189, Straub, 1900, Wislocki and O'Connor). We know also that when a man has been purged, his bowels are not likely to move for a few days. This has been supposed to be due to an astringent or constipating action of the purge, but I have considerable evidence to show that it is due simply to the lack of tension in the colon. The bowel has to fill up to a certain point before the muscle fibers will be stretched enough so that they will contract well. As Cannon has pointed out, these reactions to stretching are purely local and are not brought about by nervous reflexes.

Response to Direct Irritation. Smooth muscle shortens also under the influence of direct irritation. Thus we find spasmodic contraction of the cardia, pylorus, ileocecal sphincter and anus when there is ulceration or inflammation near by. We find hourglass contractions of the stomach opposite ulcers on the lesser curvature; and a shrunken and

irritable cap with ulcers in that region. From a diagnostic standpoint it is unfortunate that carcinomatous tissue often fails to stimulate the muscle in this way. Particularly in the colon, where the muscle is most sluggish, carcinomas will often remain symptomless until they block the lumen mechanically. Some of the sphincter spasms that are seen with inflammations or ulcers in various parts of the digestive tract may be due simply to a greater irritability of the sphincters as compared with the rest of the gut. With a lower threshold they would be very likely to pick up and respond to stimuli which are ineffective for adjacent muscle fibers. As I shall point out later in Chapter XII, the muscle fibers in the pyloric sphincter actually are more irritable than the fibers in the rest of the antrum (Alvarez, 1916[b], p. 326).

Those who would like to go more fully into the physiology of smooth muscle can get an entrée into the subject by reading the encyclopedic articles of Grützner (1904), Schultz (1895, 1903), Evans (1926), and Trendelenburg (1917[a]).

CHAPTER V

THE EXTRINSIC NERVES AND THEIR FUNCTIONS

Anyone who will wade through the extensive literature on the innervation of the digestive tube will, I think, be impressed with the fact that much of it is composed of repetitions and the rest is largely a maze of contradictions. (See Spadolini's 330 references, 1916, also Koennecke, and Koennecke and Meyer.) So many workers, unfortunately, seem to begin without first making that survey of the field which would enable them to see where further work, and especially work with a more refined technic, is needed. In many cases the same amount of energy devoted to a study of the behavior of the tract itself would probably have given more interesting and more immediately valuable results.

The Peculiar Response of Smooth Muscle to Nervous Stimulation. A great difficulty with a number of these workers and with most of the clinicians who quote from them is that they do not seem to realize that tubes like the intestine, which are lined with smooth muscle, haven't a nerve supply in the sense that a bit of striated muscle has. If one stimulates the nerve to a striated muscle, one gets a definite twitch which can be reproduced time and again in practically the same form, but if one stimulates the vagi or the sympathetics, one gets varying mixtures of weak inhibition and stimulation which cannot later be duplicated with any degree of certainty or precision (Cannon, 1911[a], May, Kelling, 1903, Thomas, 1926, Weil, M'Crea and M'Swiney). With the next stimulus there may be no effect, or the combination of inhibition and contraction may be just the reverse of what it was before. With a little difference in the strength of the stimulus, or with a difference in its rate, if it happens to be an intermittent one, different effects, again, will be produced. If the muscle is stimulated while it is in a state of high tone it may relax, but if it is stimulated when it is relaxed, it is likely to contract.

The first effect of stimulation of the vagus is generally a slight lowering of the tone of the stomach or bowel and this is followed in a few seconds by an increase in tone and activity which may last for from a few seconds to a minute. Spadolini (1916, 1917) and others have shown, however, that one can get purely inhibitory effects by stimulating the vagus, just as one can get purely augmentatory effects by stimulating the splanchnics. Ordinarily the main effect of

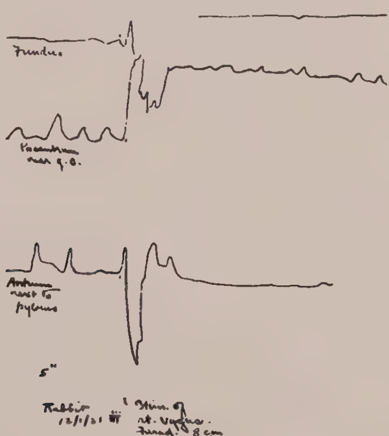

FIG. 3. Kymographic records from three points on the fundus, preantrum and pyloric antrum of a rabbit's stomach. On stimulating the vagus there were marked contractions of the fundus and preantrum and a marked relaxation of the antrum a few centimeters away.

stimulating the splanchnics is an inhibitory one. That is the effect which predominates in most animals when the abdomen is open and the nerve endings in the muscles and in the peritoneum are stimulated by trauma and exposure. The inhibitions, also, which are produced by fear, worry, and illness probably travel by way of the splanchnics.

As can be seen in Figure 3, stimulation of one vagus may cause one part of the stomach to contract while another is relaxing. Weak currents tend to inhibit contractions, while strong ones are more likely to produce them. According to Bercovitz and Rogers, a tetanizing current usually stimulates, while an interrupted one tends to inhibit. The effects

vary in different animals, so that Bunch could say that the main effect of splanchnic stimulation is inhibitory in the cat and augmentatory in the dog.

Physicians not only fail to note that the digestive tract does not respond to stimulation of its nerves in a clear-cut way, but they, and even the physiologists, seem commonly to forget that the effects of the normal stimuli which presumably flow as a gentle stream from receptors throughout the body to the ganglia of the brain and cord, and from thence to the stomach and bowel, may not be at all comparable with those of the powerful traumatizing stimuli which are obtained from the usual faradic coil. We know so little about this stream of stimuli, what it does, and how it varies, that as yet we can hardly theorize about it.

The Vagi and the Splanchnics are Mixed Nerves. Still another point which is generally lost sight of is that the vagus is not a comparatively simple or homogeneous nerve like the motor roots supplying the voluntary muscles. It is a plexus; a bundle of nerves of all sorts and sizes, medullated and non-medullated (Chase, Barratt, Edgeworth). Most of the fibers probably are connector neurones running from the brain to motor ganglia in Auerbach's plexus, but there are also afferent or sensory neurones, and even some sympathetic fibers (Miller, Neumann, Gaskell, 1916). Similarly, a "sympathetic" nerve in the abdomen may consist of preganglionic and postganglionic fibers to muscles, fibers to blood vessels and glands, and even sensory fibers belonging to the central nervous system (Gaskell, 1916, Laignel-Lavastine). It must not be forgotten also that the fibers in the vagus, unlike those in a motor nerve, do not run to the muscle. They go only as far as the ganglia of Auerbach's plexus, which can account, again, for the irregularity in the effects of electrical stimulation.

The Nature of the Involuntary Nervous System. One of the strongest objections to the recent theories in regard to the autonomic and sympathetic systems is that they make it appear that the sympathetic nerves, with the celiac ganglia, constitute a separate and distinct brain system which can be antagonistic to, or out of harmony with,

the central nervous system. This view is entirely at variance with the facts which have been collected and discussed in a masterly way by Gaskell (1916) in his monograph on "The Involuntary Nervous System." He shows that the involuntary nerves and ganglia are a part of the central nervous system; that they are connected with it just as the voluntary nerves are, and that they have developed from the same embryonic cells (Abel). The main difference is simply that

Fig. 4. W. H. Gaskell.

the motor ganglia, which in the voluntary system are found in the anterior horns of the cord, have migrated; some as far as the paravertebral ganglionic chain; some into the solar plexus, and some into the nerve nets in the walls of the hollow organs. Hence it is that the rami communicantes or preganglionic fibers in the vagus are simply elongated connector neurones such as we find between the motor and sensory roots in the cord, and in the pyramidal tracts. Furthermore, it has been shown that there are no commissural fibers between the different sets of sympathetic ganglia such as would have to be present if these ganglia were to mediate reflexes like an abdominal brain (Johnson, Langley, Carpenter and Conel). We see, then, that the involuntary system is simply a part of the voluntary system characterized by the outward migration of the motor ganglia and the necessary

lengthening of the connector neurones. On the sensory side there is no difference between the afferent fibers in a sympathetic nerve and those in a spinal nerve; they both go to the posterior root ganglion in the cord (Langley, 1905, p. 17).

THE FUNCTION OF THE INTESTINAL NERVES. We learn then from Gaskell the same lesson that we have learned from Loeb and from Parker: that the nerves are there to conduct, and not to exercise faculties requiring almost human intelligence. There are times when the animal as a whole needs to communicate with its digestive tract; there are times also when the tract must communicate with the body. There are many times when one end of the tract must communicate with the other; and on all these occasions the extrinsic nerves come into play. The vagi carry feelings of hunger and of satiety from the stomach to the brain; they help in adjusting the tone of the gastric wall to the food coming down the esophagus (Cannon, 1911[a], p. 200); and they carry the stimuli that give rise to the psychic secretion of gastric juice. If the food must be rejected by vomiting, they carry the impulses which bring the abdominal muscles to the aid of the stomach. Moreover, they probably carry messages from the digestive tract which make the animal feel comfortable and sleepy (Loeb, 1900, p. 96). The splanchnics serve largely to quiet the tract and to stop digestion when the body is distressed or injured (Cannon, 1909). The extrinsic nerves probably have much to do with the digestive upsets associated with disease elsewhere in the body but, as will be shown later, such upsets can be accounted for also by actual damage to the gastrointestinal muscle.

PSYCHIC EFFECTS. Reasoning teleologically, it is hard to understand why the digestive tract should be so subject to nervous inhibitions, because when a man is face to face with illness, danger, or any situation that can give rise to worry and fear, he has need for a good digestion, not only to keep up his strength, but his courage. Yet, in such situations, one finds many persons who are greatly hampered and handicapped by a digestive tract which either refuses to do its work, or else does it poorly. One of the great triumphs of medical research would be the discovery of some method of

blocking these troublesome inhibitions. They are annoying if only because they interfere so markedly with the individual's confidence in himself. The "all gone" sensation in the pit of the stomach, the faint waves of nausea, and the unstable vasomotors all contribute to a feeling of impending disaster which strikes fear into the strongest heart. Actually, it may be that the first and principal requisite for bravery is an immunity to splanchnic inhibitions and to the unpleasant effects of the epinephrin which Cannon believes is poured out during times of stress.

This influence of the emotions on digestion, with the resultant flatulence, borborygmi, and loosening of the bowels probably accounts for the fact that many primitive peoples locate the soul in the abdomen. The idea still survives in such phrases as "bowels of mercy" or "he hasn't the guts."

THE EFFECTS OF CUTTING THE NERVES. The differences between the functions of nerves supplying voluntary and nerves supplying involuntary muscles, emphasized at the beginning of the chapter, stand out even more plainly, perhaps, when one comes to study the effects on the stomach and bowel of cutting the vagi and the splanchnics. As is well known, when a voluntary muscle loses its motor nerve it becomes permanently paralyzed and soon atrophies. On the other hand, as has been mentioned in Chapter I, when the nerves to the digestive tract are cut, little happens. There is a short interval during which the muscle may be somewhat atonic and during which peristalsis is shallow, but later, in many of the experimental animals, little difference from the normal can be made out. I refer of course to experiments in which the vagi are cut below the diaphragm. When they are cut in the neck, that part of the esophagus that is supplied with striated muscle does not regain its function, and the animal dies unless it is fed with great care.

According to M'Crea, M'Swiney and Stopford, who have gone into the problem very carefully, animals in which the vagi have been cut below the diaphragm fall into two groups: one with temporary disability and the other with permanent disability. In the first there is dilatation and paresis of the stomach, and in the second there is perhaps slight dilatation

with an increase in the depth of peristalsis. Such stomachs empty rapidly at first and a little more slowly toward the end; the sphincter of the pylorus seems to be patulous and food pours out of the stomach. Differences from this picture may be seen in animals in which the operator failed to cut the branch which supplies the pylorus.

The idea which many have that in health there must be a balance between the influences on the bowel of the vagi and the sympathetics receives some support from the fact, noticed by several workers, that when all the extrinsic nerves are cut, gastrointestinal peristalsis is more nearly normal than when the vagi alone are removed. A slowing of gastric emptying after section of the vagi would seem, then, to be due not only to the loss of tonic influences coming down those nerves, but also to a preponderance of depressive stimuli arriving by way of the splanchnics. Miss Mahoney and I found that after section of the vagi there was less tendency for rush waves to start off down the bowel and it was harder to make them go, which fits in with Cannon's observation that under these circumstances food goes down the intestine more slowly. When he cut the splanchnics, he found it went through more rapidly (1906[a], p. 436), and others have observed the same thing.

Cutting the Nerves in Man. Zesas has culled from the literature a large series of cases in which, in men and women, one or both vagi were severed by operations, injuries, or by malignant growths, and so far as I can judge from his review, there was seldom any effect on digestion. According to Leriche, there may be vomiting and colic when the vagi are pressed upon by scar tissue in the chest. There is some evidence that damage to the abdominal sympathetics will produce disturbances of digestion, but more careful case and necropsy reports are needed before any definite syndrome can be established.

The large nerves which course along the lesser curvature of the stomach are being removed now in hundreds of men and women who have to submit to subtotal gastrectomy, but the end results are generally good; peristalsis seems to be normal, and the only change is in the gastric acidity which is reduced,

sometimes to the vanishing point. Cohn studied the after-result in the case of a woman whose stomach, together with large sections of both vagi, was removed for cancer. She experienced no hunger and no feeling of fullness but at times was conscious of the fact that the food was not moving onward as it should. On such occasions she was able to regurgitate considerable amounts of what she had eaten,

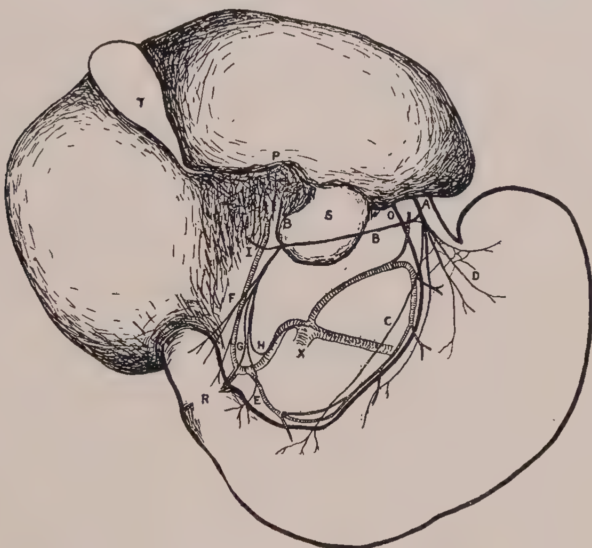

FIG. 5. Drawing to illustrate the distribution of A, the anterior vagal trunk. B, the hepatic branch. C, the principal anterior nerve of the lesser curvature. D, gastric branches. E, pyloric branch. F, duodenal branch. G, branch with gastroduodenal artery. H, branch passing proximally on hepatic artery. I, branch to gallbladder. X, celiac axis. P, porta hepatis. S, caudate lobe. T, gallbladder. O, esophagus. R, pylorus. (*From M'Crea.*)

apparently without the help of the voluntary muscles. Roentgenoscopic examination showed that food went slowly through the esophagus and bowel. She was badly constipated.

It should be noted here, however, that the excision of the nerves along the lesser curvature need not affect the vagal supply to the bowel, unless damage is done to those fibers which run from the posterior surface of the stomach near the cardia to the solar ganglia. Figure 5, taken from the

excellent study by M'Crea, shows that the vagus does not run from the stomach down over the pylorus and into the bowel, but that the pylorus and duodenum get their supply from a branch that goes to the liver (Brandt). The small intestine receives a large branch in the region of the upper jejunum (Bayliss and Starling, 1899, Mackenzie, 1916, 1917, Jacobj, 1891, Poirier and Charpy).

It does not seem likely that the extrinsic nerves can have anything to do with the rates of rhythmic contraction in the various parts of the stomach and bowel, and no one has ever been able to detect any such chronotropic effect as is seen after the nerves to the heart are stimulated.

7 *Reflex Inhibitions.* Lehmann, Hotz, L. R. Müller, 1911, and others have shown how easy it is to inhibit the movements and to lower the tone of the digestive tract by stimulation of almost any one of the nerves of the body. Cannon and Murphy showed years ago that crushing injuries to the testis can produce dynamic ileus, and surgeons know that the stomach will sometimes dilate, or the bowels become atonic after operations on the kidneys or other organs situated outside the peritoneal cavity.

Pearcy and Van Liere have shown also that sudden distention of almost any part of the digestive tract will inhibit for a few moments the activities of all other parts, and that the paths for these stimuli are in the cord and the mesenteric nerves and not in the wall of the bowel. Similar impulses perhaps account also for the inhibition of the hunger contractions of the stomach (Carlson). Such inhibition can be produced by stimulation of the mucosa of the stomach or intestine, and is dependent to a considerable extent on the integrity of the extrinsic nerves. When they are cut the effects are weaker and the latent period longer, which suggests that conduction has then to take place more slowly through the less efficient nerve net.

The nerves in the mesentery may serve also to produce the "gastrocolic reflex" of Hurst in which the emptying of the stomach tends to hurry the emptying of the ileum into the colon; and they may serve to transmit messages in the opposite direction that help the stomach to empty when the

ileum has discharged its contents. They do not seem to have anything to do with forwarding or directing peristalsis in the bowel because when I (Alvarez, 1924[c]) cut the intestine across and watched rush waves running down to the opening, I could detect no change in the activity of the segment just below the wound, unless I had, in some way, connected the two ends. I did suspect, however, that messages were being sent up and down the mesentery because at times there were simultaneous contractions of many parts of the gut, or more or less simultaneous rises in tone, or rises in tone appearing ahead of rushes and serving to stop them. Several observers (Surmont and Dubus) also, have been able to affect the activity of the colon by stimulating the stomach or vice versa, even after they cut the ileum in two.

Connections with the Brain. The nausea and vomiting of seasickness are due probably to stimuli arising in the vestibular apparatus and traveling down the vagi. In migraine, similar upsets seem to be due to stimuli coming from an irritable spot, perhaps in the sensory area of the brain; and projectile vomiting is seen with increased intracranial pressure.

According to some investigators (Preiss) the vagi carry no pain-perceiving fibers, but Exner and Schwarzmann claim that half of the patients with tabetic crises can be cured by cutting either the vagi or the posterior roots of some of the nerves leaving the lower dorsal cord. These workers cut the vagi in 14 patients without causing any disturbance in digestion. Borchers (1921), however, after reviewing the literature on this subject came to the conclusion that little can be hoped for from such operations. He cut the vagi in cats and later watched gastric peristalsis through celluloid windows which had healed into the abdominal wall. He found that when he irritated the mucous membrane of these stomachs or made ulcers, he produced the same amount of spasm as he had seen in similar experiments with animals with the vagi intact. Incidentally, these observations make the attempts to reduce spasm in the digestive tract with the help of atropin look rather hopeless.

In some of the patients with headache and indigestion the impulses are probably traveling from the digestive tract to the brain. This seems to take place most frequently with disease of the biliary apparatus, and with distention of the duodenum and rectum. I am inclined to think that much of the shock seen with high intestinal obstruction is due to the powerful stimuli which are sent to the brain when the duodenum and jejunum struggle incessantly to empty themselves. Normal peristalsis in the jejunum is apparently sedative, as was shown by a patient of mine on whom jejunostomy had been performed for feeding purposes. When I put a little balloon into his jejunum, he often went to sleep much as he would after a good meal. One of the most striking symptoms in cases of chronic duodenal stasis is said to be headache.

Gaskell (1916) has suggested that painful stimuli traveling up the vagi may cause headache by crossing over to the closely related nuclei of the trifacial nerve (Head). Such crossing would account also for the stabbing pain in the forehead which many persons feel when they drink ice water. I have seen patients with acute disease in the gall bladder or stomach experience pain and tenderness in that region behind the ears which is supplied by the vagi, and similar observations have been made by others (Rasdolsky). Sherrington has described the fibers involved and believes them to represent the nerve supply to the first branchial cleft. Incidentally, it may be of interest to note that in certain fishes the nuclei of the vagus and trigeminal give off enormous branches which run the length of the animal and supply the skin.

Carlson (1916) has pointed out, also, that the hunger contractions of the stomach increase the reflex excitability of the central nervous system. They increase the rate of the heart beat, they affect the vasomotor mechanism, and they increase the flow of saliva.

While experimenting with animals I have been impressed time and again with the fact that powerful contractions of the stomach or the handling of that organ are likely to produce gasping or slight struggling as if the animal were going to

wake from the anesthetic. As in such experiments the spinal cord was generally destroyed in the lower dorsal region, the only pathway to the brain must have been along the vagi. Ranson believes that although afferent impulses from the digestive tract often reach consciousness as painful sensations, most of them do not emerge that far but expend themselves in the production of reflexes. Certainly we will all agree that at times, as before dinner, they can profoundly affect our sense of well-being, and can make of us either good-natured optimists or ill-tempered, irritable pessimists.

Nerves to the Colon. As Carlson (1916) has pointed out, it is questionable whether vagus fibers reach the large intestine. This may be because in some of the earlier forms of life such as the dogfish, there is no colon, and the vagus supplies all of the bowel that there is. Later, in higher animals, when a colon develops it has to find its nerve supply in the sacral region. This of course is hypothesis, and I do not know enough about the comparative anatomy of the vagus to know whether it is probable or improbable. According to Elliott and Barclay-Smith, the pelvic nerves are distributed only to the lower two-thirds or three-fourths of the colon. In the cat and rabbit, the cutting of the sympathetic fibers to the colon causes no lasting disturbance in the motor functions but after the cord has been destroyed or the pelvic nerves cut, the function of defecation is disturbed. Further details in regard to this will be found in Chapter XX.

CHAPTER VI

WHY FOOD GOES DOWN THE BOWEL

The most important problem that daily faces the gastro-enterologist is: Why are there abnormalities in the progress of the food and its residues through the digestive tract? Why do they linger too long in some places, and why is the current so often reversed, as evidenced by regurgitation, belching, nausea, and vomiting? Before the clinician can answer these questions, and before he can tinker fairly intelligently at the workings of the digestive tube, it is obvious that he must know why food normally travels caudad; that is the most important problem before him, just as for years the normal mode of progress of the cardiac impulse was the most important problem before the heart specialist.

Bayliss and Starling's Law, or the Myenteric Reflex. If in his perplexity, the physician turns to his text-books on physiology he will doubtless get the impression that this problem of peristalsis has already been solved, and that there is nothing more that needs to be done about it. Food goes down the bowel simply because "if cerebrospinal reflexes be excluded excitation at any point of the gut excites contraction above and inhibition below"; this is the "law of the intestine" (Bayliss and Starling, 1899). Such was the conclusion of Bayliss and Starling when, in 1899 and 1901, they published their three classic articles on the movements and innervation of the bowel. Cannon later proposed the term myenteric reflex for the phenomenon which they had described, and showed that it could at times be demonstrated also in the stomach.

With this backing from three of the leading physiologists in the world it is not surprising that the law or reflex should promptly have become one of the foundation stones of physiology about which afterwards there was no question or argument. Now, while I would not think of denying that such a phenomenon ever occurs, I must point out that the

subject is not the closed chapter which most of us have assumed it to be, and that even if the law were valid, it could not explain a tenth of the problems that crowd up for solution. Furthermore, I must call attention to the surprising fact that when one turns to the articles written by the few men who studied this reflex years ago, one finds frank admissions to the effect that it was hard to demonstrate, that it was often absent, and often reversed.

Bayliss and Starling point out that the reaction generally takes place within a few centimeters of the stimulated

Fig. 6. Sir William M. Bayliss.

point. The inhibition below is confined mainly to the circular muscle, and it is often absent. "In many cases, however, our results have not been quite so clear. Although stimulation above the balloon produced inhibition, stimulation below produced also inhibition or preliminary inhibition followed by contraction." Again: "The two effects do not run absolutely parallel to one another, in that in some experiments the inhibitory effects from above, in others the augmentor effects from below, may be better marked." These troubles persisted even after the extirpation of the abdominal ganglia. In another paper they admit that when they changed from

dogs to cats they did not get good pinch reactions, according to the law, until they remembered that they had always given the dogs a preliminary dose of castor oil. Even when they gave this drug to the cats they did not get as typical reactions as they got in the dog, and they had difficulties again when they tried to use rabbits. It seems to me that so important a law should be capable of demonstration in all of the laboratory animals without the help of drugs.

FIG. 7. Ernest H. Starling.

Moreover, Bayliss and Starling admitted that their technic could be objected to because the bowel is not normal when it has been opened for the insertion of a balloon. My own experiments with balloons so impressed me with the abnormal nature of the conditions that I felt I could put little trust in the results obtained.

Magnus (1904[a], p. 132) says he was able to show the law in excised strips of intestine stimulated with a salt crystal. He admits, however, that he could not obtain the expected reactions "with mathematical regularity." In some animals he got inhibition above and below. Langley and Magnus (p. 46) also had considerable difficulty in trying to show the law. They say: "It must be noticed that although inhibition below a point stimulated was so frequently obtained, it was in any one experiment, which lasted two to three hours, very inconstant; at one time the inhibition would be marked

and at another absent, and the period during which one or the other state supervened was sometimes at the beginning of an experiment, sometimes an hour or two later." Degenerative section of most of the superior mesenteric nerves did not abolish the reactions, showing that their mechanism is situated in the bowel wall.

Cannon realized fully that the "myenteric reflex" is not always demonstrable. "What causes [it] to appear or not

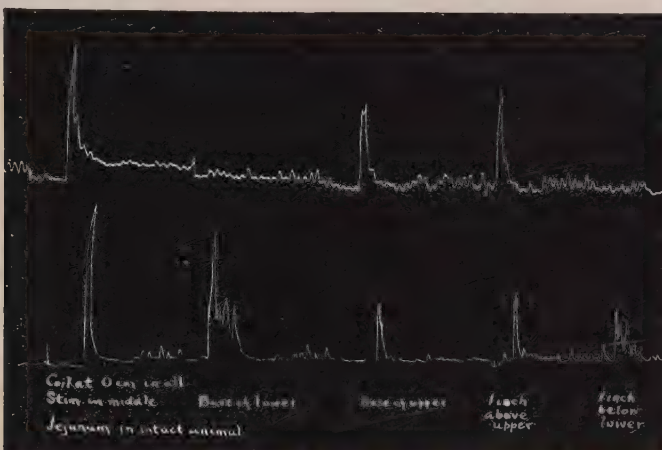

FIG. 8. A coil of jejunum 8 cm. long in an intact rabbit (abdomen opened under salt solution) was made to record at both ends. When this bowel was stimulated faradically near the upper recording thread it responded below; when it was stimulated near the lower end, it did not respond above. When stimulated midway between, the twitch at the lower end was greater. Note the absence of the myenteric reflex.

when material is present, is as yet undetermined . . . It does not govern the rhythmic contractions of the small intestine, the rhythmic peristalsis and antiperistalsis of the colon, and probably not the rhythmic waves of the stomach." (Cannon, 1912, p. 125; 1911[a], p. 195.)

Miss Starkweather and I (1919) studied graphic records of the contractions resulting from more than 2000 stimuli (mechanical, electrical, and chemical) applied to the intestine (mainly of rabbits) and found that the usual response in all but about twenty of the experiments was a contraction

above and below (Fig. 8). Most of the few responses that corresponded to the law were obtained by distending the bowel with a small balloon. One objection that may be made to our experiments is that in most of them the records were taken from the longitudinal muscle, while Bayliss and Starling got their results mainly with the circular.

The Normal Rush Waves. Another objection that can be made to all the work done so far is that the stimuli used were abnormal. What the physiologist and the clinician need most is information as to how the bowel behaves during the progress of the normal rush waves which have most to do with passing food residues down the bowel. It seemed to me that if descending inhibition has any significance at all it should be demonstrable ahead of these waves; hence, Miss Mahoney and I (Alvarez, 1924[c]) spent two years in collecting and studying records depicting their progress down the bowel. As a result we could say that there was a preliminary widening of the bowel in only one out of six of the tracings. In 38 per cent there was a gradual rise in the tone of the bowel for from ten to twenty seconds before the crest of the wave arrived. No inhibition could be detected in another 27 per cent; a slight questionable inhibition was found in 20 per cent, and a definite drop in the level of the record or, more often, an inhibition of one or two rhythmic contractions was found in 15 per cent. In a large number of cases, therefore, there was a preliminary rise in tone, which is just the opposite of what the law requires; and there was never any sign of such inhibition as one would think would be necessary really to assist in the forwarding of the intestinal contents. The big drops in tone came just after the waves had passed, but that was due to the emptying of the bowel.

When I reported this work in 1924 I expressed my doubts as to the nature of the preliminary widening of the bowel which appeared in the records; I was inclined to regard it as due not to inhibition but to distention by the long column of intestinal contents which is forced ahead by the wave of contraction, much as a train of cars is pushed up a grade by an engine at the rear. Recently, with the help of motion pictures, Dr. Zimmermann and I proved that this suspicion

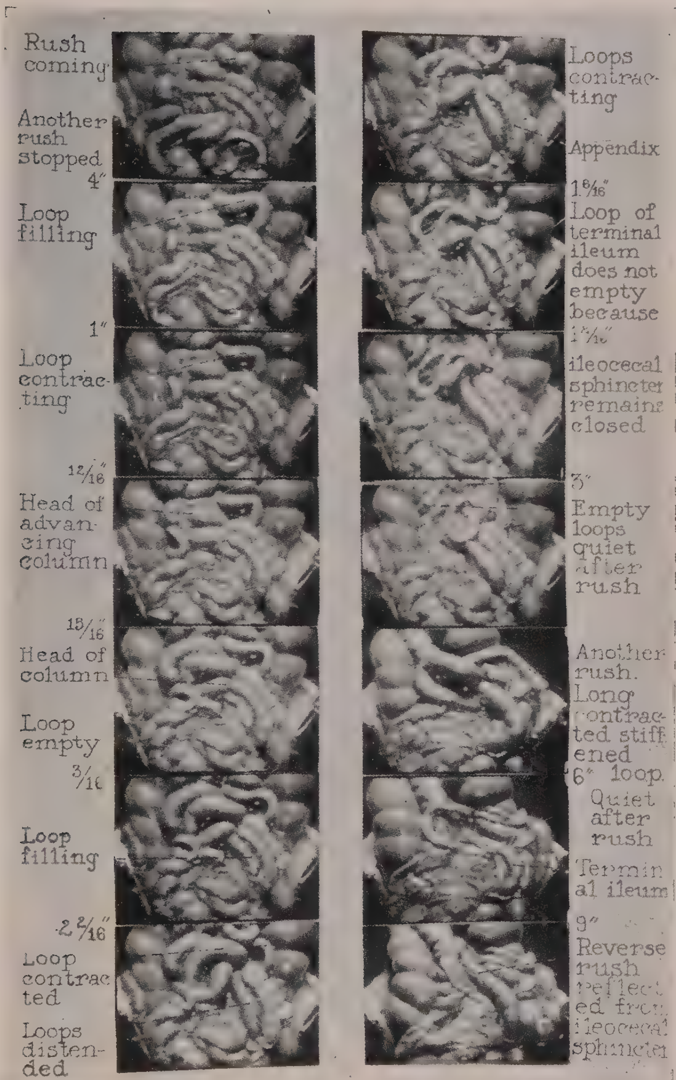

FIG. 9. Peristaltic rush in a rabbit; pictures reproduced from a cinematographic film. The figures represent the number of seconds elapsed between the taking of the pictures.

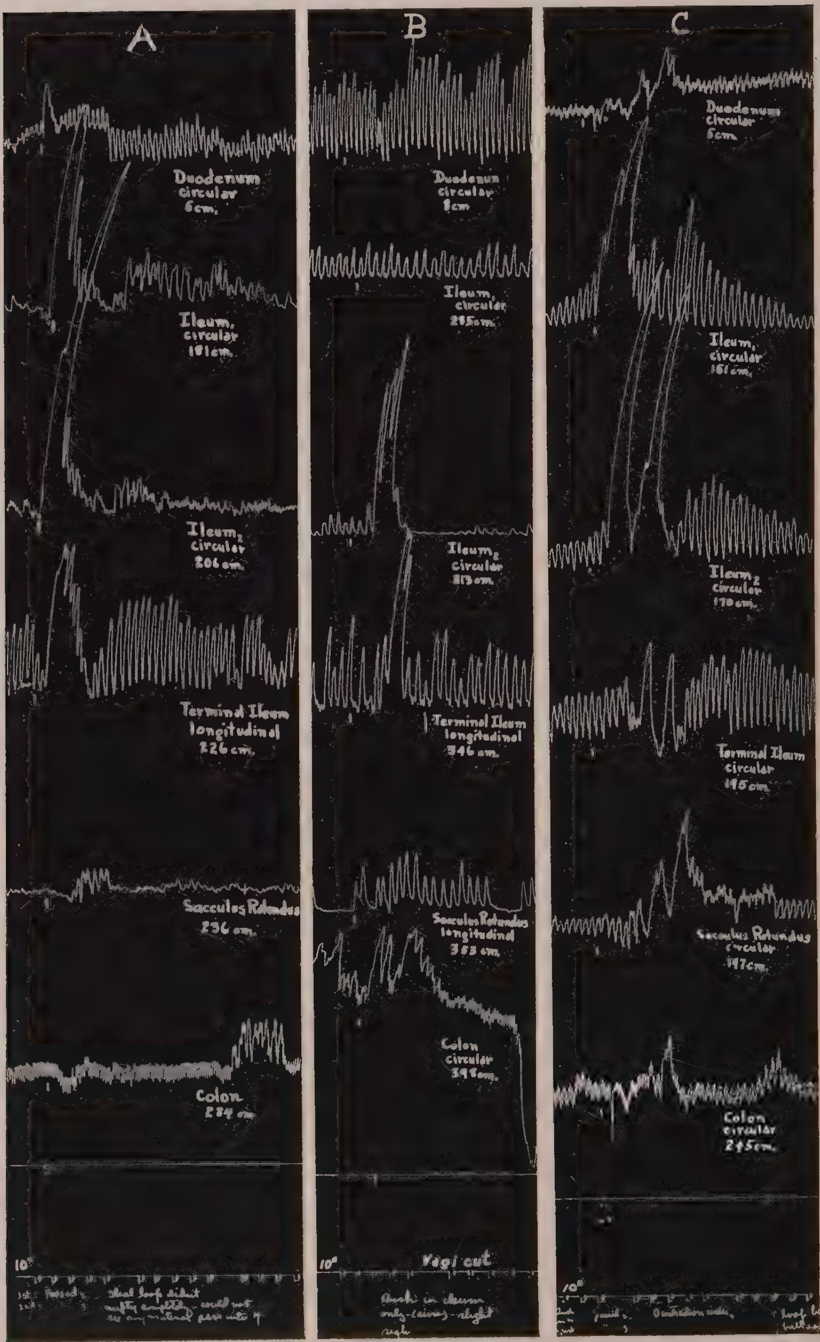
A
B
C
Duodenum circular 6cm.
Ileum, circular 181 cm.
Ileum₂ circular 206 cm.
Terminal Ileum longitudinal 226 cm.
Sacculus Rotundus 236 cm.
Colon 254 cm.
Duodenum circular 8cm
Ileum, circular 215 cm.
Ileum₂ circular 313 cm.
Terminal Ileum longitudinal 346 cm.
Sacculus Rotundus longitudinal 353 cm.
Colon circular 398 cm.
Vagi cut
Duodenum circular 5cm.
Ileum, circular 161 cm.
Ileum₂ circular 170 cm.
Terminal Ileum circular 195 cm.
Sacculus Rotundus circular 197 cm.
Colon circular 245 cm.
10"

FIG. 10.

was correct, and that the widening of the bowel ahead of the contraction is due to distention and not to inhibition. By measuring the diameter of the gut in successive pictures and plotting those distances as ordinates, with time intervals as abscissas, we obtained graphs like the one reproduced in Figure 12 which show that the lumen of the bowel does not widen until the intestinal contents are forced into it.

A Dissociation between the Wave in the Muscular Wall and the Progress of Contents in the Lumen. Bayliss and Starling felt so sure of the importance of their law that they were willing to say that when either the contraction above or the inhibition below is absent, "the onward movement of the bolus becomes impossible." It is interesting to note, however, that in one of their experiments when the reflex was abolished through fatigue and the bolus would no longer budge, a peristaltic wave still went over it and on down the bowel (1899, p. 108). That is just the sort of thing that Miss Mahoney and I observed repeatedly: a dissociation between the wave of contraction in the muscle layer and the movement of the material through the lumen of the bowel. It is a point of great importance which has not been recognized in the past. A somewhat similar phenomenon is seen in the stomach where, as every roentgenologist knows, only a few of the waves running over the pars pylorica grip the contents and pass them onward. Others, apparently just as powerful, have no effect. It makes one think of some sort of a clutch which can be let in to connect the intestinal engine with the work it has to do. The work with the motion pictures shows now that many of the differences in the appearance of the mechanical records of even one and the same rush, passing several points on the bowel, are due simply to the fact that at times it pushes material before it and at other times it does not (Fig. 11).

FIG. 10. A shows rise in duodenum synchronous with rush in lower ileum. Material was all left behind at a point 226 cm. from the pylorus, and only a ripple went on; B shows drop in amplitude in the duodenum as a wave goes down the ileum; C shows rise in duodenum shortly after a rush in the lower bowel. The big rises in the tone of the sacculus often stop the rushes.

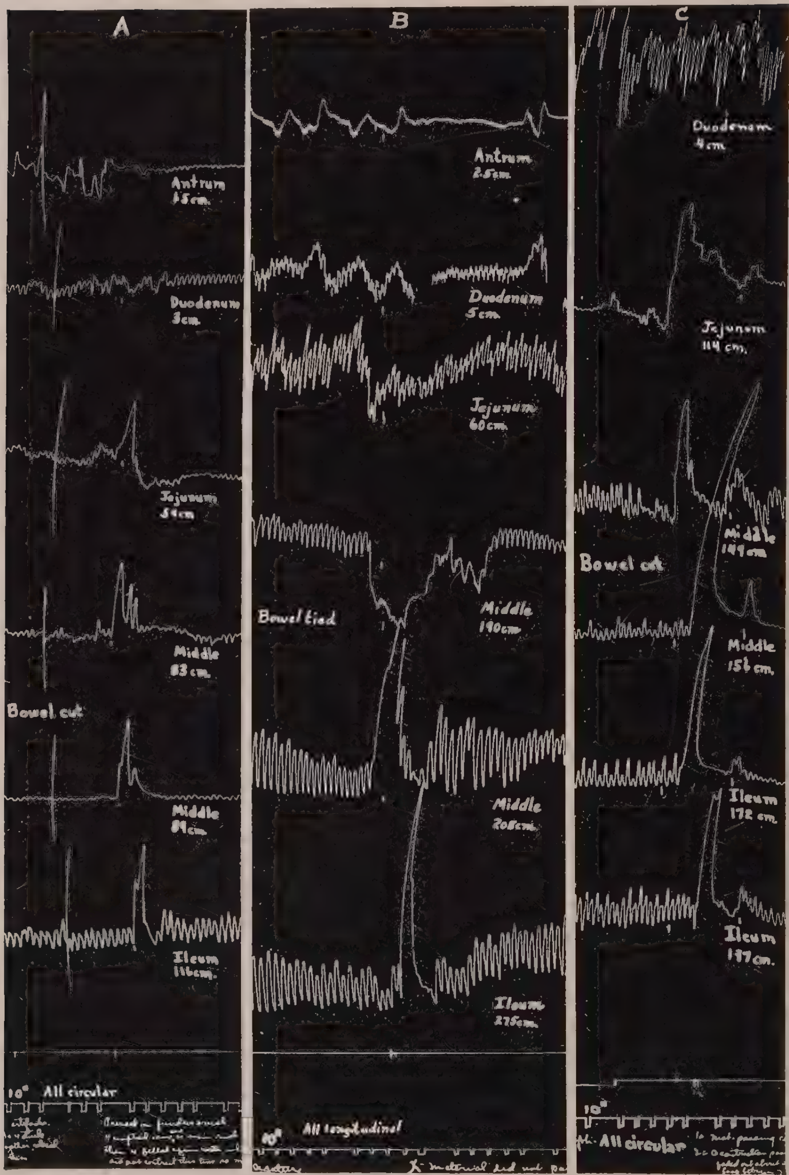
A
Antrum 15cm.
Duodenum 3cm.
Jejunum 54cm.
Middle 83cm.
Bowel cut
Middle 91cm.
Ileum 116cm.
10"
All circular
B
Antrum 2.5cm.
Duodenum 5cm.
Jejunum 60cm.
Bowel tied
Middle 190cm.
Middle 208cm.
Ileum 275cm.
All longitudinal
C
Duodenum 4cm.
Jejunum 114 cm.
Middle 149cm.
Bowel cut
Middle 156 cm.
Ileum 172 cm.
Ileum 197 cm.
10"
All circular

FIG. 11.

Rushes Can Jump Gaps or Obstructed Places in the Bowel. When a number of recorders are attached along a loop of bowel it is easy to show that not only will a rush wave go on down the bowel after it has left the burden of its contents behind, but the contents will go on down and pick up a new rush wave after they have left their old wave behind. In the first experiment a piece of tape is tied lightly around the bowel so as barely to occlude its lumen, and in the second, the bowel is cut in two and the ends tied over a short piece of glass tubing. Figure 11 shows that in either case the waves go on down the bowel with little or no hesitation.

In designing the second experiment I had in mind the work of Friedländer who cut an earthworm in two and tied the pieces together with a bit of thread. The hind end crawled on in coordination with the front end simply because the rhythmic pulls on the string supplied the necessary stimuli to the underlying muscles.

Miss Mahoney and I showed that downward peristalsis can take place not only without the help of any myenteric reflex, but even when the bowel ahead is powerfully contracted. Actually, of course, it is fortunate for us that the bowel ahead does contract and does try to stop the rushes because if the myenteric reflex were always at work, the intestine would promptly be emptied and we should die from diarrhea and starvation.

I see no reason why the wave in the wall of the bowel should not travel very much as does the impulse in the heart, with the action currents spreading out ahead in some such way as Lillie has described. The direction of spread is probably determined, as in the heart, by gradients of rhythmicity and metabolic rate, and so far as the muscular ripple in the

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FIG. 11. A. The bowel was cut across and the ends tied over a piece of glass tubing 3.5 cm. long and 5 mm. in inside diameter. A rush passed; the bowel below the tube contracted two seconds before the constriction reached the upper end, showing that a new wave arose in response to the arrival of material from above. B. Shows a rush wave continuing after it has left its freight of intestinal contents above an obstruction. Note drop in level of the fourth record due to distention of the loop. C. Shows a rush traversing a section of bowel which has just been cut in two and then sewed together again, end for end.

intestinal wall is concerned, it probably has no more need of descending inhibition than has the wave in the heart. So far as I know, no one has ever felt called on to postulate a myenteric type of reflex in that organ.

Difference between the Transport of Solids and Fluids. As will be pointed out in more detail later, there is probably a difference between the problems involved in the passage

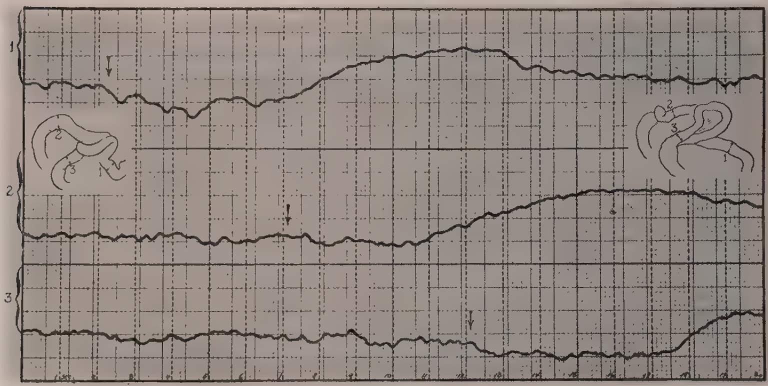

Fig. 12. Shows the absence of descending inhibition as a peristaltic rush swept through three adjacent loops of ileum. The small diagrams show the appearance of the loops in the abdomen and the places where the three diameters were measured in 320 successive pictures in a cinematographic film. The spaces between the bracketed lines, one straight and the other wavy, represent the varying diameters of the bowel at the three points. The wavy lines correspond to those that would have been obtained if threads had been run from the bowel to levers recording simultaneously on a kymograph. The record reads from left to right; a drop in the line indicates relaxation or distention, and a rise indicates contraction. The vertical dotted lines represent intervals of 1 second. The arrows indicate the moment when the head of the advancing column of fluid appeared in the picture. The small irregularities in the record are probably not significant.

of solids and fluids through the intestine. These problems are comparable perhaps to those involved in passing rocks and water through a pipe line. The water will go anywhere, up hill and down, if enough pressure is put on it, but the rocks will go only down hill. Similarly in the bowel, liquids will flow for considerable distances without the help of any rush

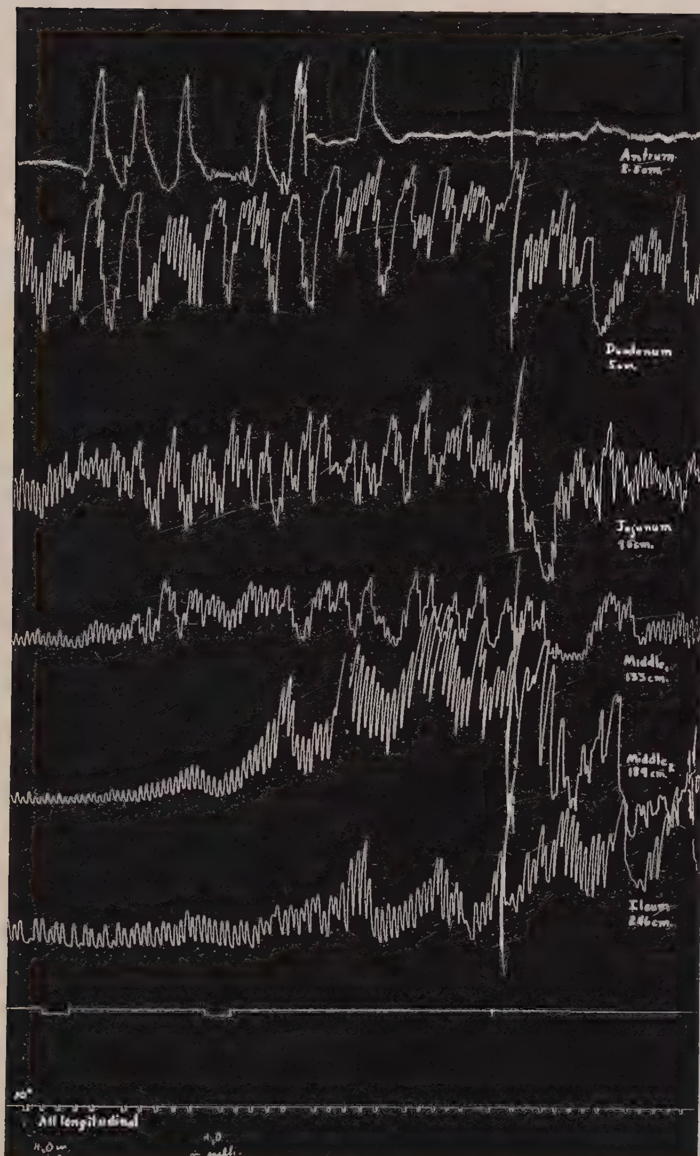

FIG. 13. Shows the increase in the intestinal activity and the rise in tone which took place when considerable fluid seeped slowly down the bowel. Note the drop in level when a rush came and partly emptied the loop 189 cm. from the pylorus.

waves (Fig. 13). For that matter, water can be pumped into an animal's rectum until it flows out of the mouth, and Müller and his associates have shown that even after all the muscle has been stripped from long stretches of bowel, dogs will live comfortably if kept on a low-residue diet. Returning to the simile of the pipe line, fluids can evidently be passed through long stretches where there is neither gradient nor motive power.

Why Rushes Can Overcome Obstructions. If one watches a rush wave in a rabbit one can see that the column of intestinal contents traveling ahead of the contraction ring is several centimeters long. With the motion pictures it can be shown that it usually takes about six seconds for this column to pass a given point, and as it travels with an average rate of about 6 cm. a second, it is obvious that it must ordinarily be about 36 cm. long. The bowel then remains contracted for from ten to twenty-five seconds, during which time the head of the column can advance for a distance varying between 60 and 150 cm. Actually, it may go even farther because by the time some of the rushes reach the ileum, they are traveling 20 cm. a second. Under these circumstances it can easily be seen that once a wave is started in one direction it must continue in that direction so long as the bowel is irritable enough to respond locally to the presence of the column of fluid, and so long as the resistance ahead does not become too great.

Why Rushes Travel Caudad. The next question is: How does it get started in the caudad direction? Material put into the middle of the bowel should, with this mechanism alone, go equally well in both directions. Actually, it does tend to do that, but probably on account of the presence of the gradient (Chap. VII), it is hard for the wave in the muscle to run orad and it soon fades out. The caudad wave running with the gradient gathers momentum and runs faster the farther it goes. Matters are simpler probably when the rush starts, as it usually does, from the pylorus, which can close behind it and can prevent regurgitation. To use a Hibernianism, food goes down the bowel more easily because it is put in at the upper end.

Theoretically, then, if we were to put irritating material into the terminal ileum and then to close the ileocecal sphincter behind it we might produce a reverse rush. Actually I have been able to do this in two cats by first raising the irritability of the colon by causing it to contract powerfully on some soapy water. This water was injected and the rectum then tied off. In one case the ileocecal sphincter leaked, and in the other I injected some of the colonic contents into the terminal ileum. The resultant wave, which ran up as far as the duodenum, seemed very plainly to be due to the irritation of the bowel as the soapy colonic contents reached successive loops. The column had to move orad

Fig. 14. Sir Arthur Keith.

because the bowel behind it remained contracted for so long a time that there was no chance for any regurgitation. Recently, in a cat with a poor rhythmic gradient (for the meaning of that word see Chap. vii), I obtained records of spontaneous reversed rushes running from the ileum to the stomach and producing vomiting. Figure 84 shows that the records of these reverse waves are practically the same as those of the descending waves.

The Cause of Downward Peristalsis Not Simple. It seems obvious from all this that the problem of intestinal peristalsis is not so simple as we have thought it in the past, and that there is much more to it than can be explained by the myen-

teric reflex, even if one could regularly demonstrate it. One would still have to explain the mechanism through which it is brought about, and particularly the mechanism that causes it to appear at one time and not at another. My own feeling is that the law should first of all be restated; that is, it may perhaps have to do only with the reactions of the bowel to distending foreign bodies like balloons. At least in the rabbit it certainly is not the response which follows stimulation of the outer coat of the bowel, and so far as I can see, it has nothing to do with the normal peristaltic rushes in that animal. It may possibly be peculiar to the dog, but in that case it should not be called the law of the intestine.

Keith's Theory of Peristalsis. There has recently been a tendency on the part of many men to ascribe the regulation of peristalsis to certain nodes, the presence of which have been postulated by Sir Arthur Keith. In two articles published in 1915, he reported having found, associated with Auerbach's plexus, cells which he thought were intermediate between muscle and nerve, and which were similar to those in the Keith-Flack node of the heart. Shortly after making this discovery, he read my first two communications on intestinal rhythm, and was impressed by the fact that the terminal segment of the ileum sometimes sets the pace for a short stretch of bowel immediately above. It suggested to him that the little collections of possibly nodal tissue which he had found at the cardia and ileocecal sphincter, and other collections which he did not find, but which he thought might be present in the duodenum, upper jejunum, and middle small intestine, might be centers dominating the rhythm and activity of those sections of the tract. He suggested that the "food is propelled through a series of zones or segments, each furnished with its own pacemaker and its own rhythmical contractions." Intestinal stasis, of the Arbuthnot Lane type, may be due to blocks "at the points where one rhythmical zone or area passes into the succeeding zone." Since then several writers have been much impressed with this idea, but unfortunately, they seem to have read Dr. Keith's articles only in abstract, because their published diagrams show nodal tissue at the points

where Keith says he expected to find it but did not. Moreover, they do not seem to realize that Keith made no physiologic studies, but simply threw out some suggestions on the basis of his anatomic findings.

The plausible feature in this theory is that we know that in the heart the region with the fastest rate sets the pace for the others. Although to the naked eye the heart seems to contract simultaneously all over, graphic records show that a wave of excitation travels from the sinus to the ventricles. Somewhat similarly, in the stomach, the area with the most rapid rate at the cardia appears to set the pace and we can see the waves traveling slowly to the pylorus. In the small intestine, however, each segment tends to contract at its own rate, and only occasionally do we see what are called peristaltic rushes running some distance down the bowel.

Although the duodenal muscle has the fastest rate it does not set the pace for the rhythmic contractions of the rest of the gut. I must emphasize this point because several writers in overlooking it, have theorized unwarrantedly on the basis of Keith's findings. Furthermore, Miss Starkweather and I (1919) made a careful study of the regions suspected by Keith of being pacemakers; we counted the rates of rhythmic contraction in these segments and in adjoining ones before and after cutting them apart, and we found no sign of any zones or of any rhythmic domination of one segment over another. I doubt if the ileocecal ring has much to do with the activities of the colon, because they continue as usual after the removal of the whole cecal region. Similarly in the stomach, the waves travel normally after the removal of the lesser curvature, showing that this region contains nothing that can be compared to the nodal system of the heart. Although it is often helpful to make comparisons between the activities of the heart tube and the intestine, they must be made with great care and with due regard for all the facts in the case.

Incidentally, so far as I know, no one has yet confirmed the anatomic findings of Keith. I know several anatomists who have explored sections from the stomach and bowel without

being able to satisfy themselves that anything like nodal tissue exists there.

A NEW LAW OF THE INTESTINE

If I were asked to formulate a law for the intestine, I would say that stimulation at any point leads to the holding back of material coming down from above, and the hurrying onward of material already below. Such a law would fit in much better with the facts observed not only in the physiologic laboratory but also in the clinic. What these facts are will be brought out in subsequent chapters.

CHAPTER VII

GRADIENTS

If, at a certain point, we stimulate the smooth muscle in a tubular organ like the intestine or ureter, we get a contracted tonic ring from which waves are given off in both directions (Cannon, 1908, and 1911[b], p. 419; Engelmann, 1869, p. 259; Kretschmer). These waves remind one of the concentric ripples which arise at the point where a stone has been

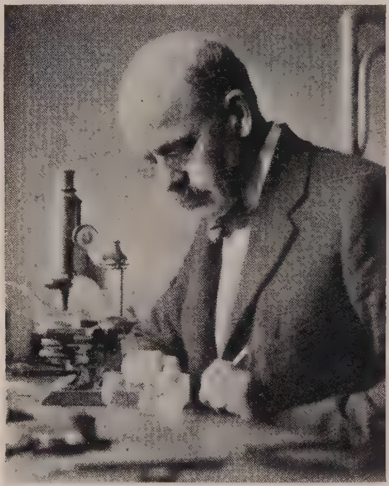

FIG. 15. Charles M. Child.

thrown into a pond, and actually the physical conditions underlying the two phenomena are very similar. In each case the level or potential is raised at one point and waves of activity flow down away from that region until an equilibrium is restored. If another stone is thrown into the pond near the first one, some of the waves approaching the second area are slowed and stopped; and similarly, if a second tonus ring is made in the bowel, the waves approaching it are blocked. They are slowed and stopped because they have, in a way, to run up hill to the second area of high potential.

One of the best ways in which to make one of these pulsating contraction rings is to touch the bowel with a crystal of barium chloride which, as is well known, raises the tone of the muscle.

C. M. Child tells me that the ripples spreading both ways from a stimulated point can be shown beautifully in some of the Ctenophores—little jellyfish with comblike rows of swimming plates which beat in a regular order from one end of the row to the other. If the midpoint of one of these "combs" is stimulated, waves of contraction in the little paddles run off in both directions, but the one traveling toward the pacemaking end is soon extinguished. Similar observations have been made by Moore (1926) on the sea pen, Pennatula, in which bars of light alternating with bars of darkness spread away in both directions from a stimulated point. Certain specimens apparently have a gradient of some kind which makes it easier for waves to pass in one direction. In one case eleven waves ascended while only three descended.

CONDUCTION

These waves spread out from muscle fiber to muscle fiber, and there is little need for any assistance from nerves, ganglia or centers. I have observed such waves (after electrical stimulation) spreading both ways along the segments of a recently voided dog's tapeworm, and I have seen them traveling away from the ridge which forms when one strikes the irritable pectoral muscles of a consumptive; yet in neither of these tissues is there anything corresponding to Auerbach's plexus. Cannon (1911[a], p. 193) has shown that peristaltic waves continue to travel over the stomach after it has recovered from the making of several cuts through the muscle and plexus down to the mucous membrane; and Meek has made similar observations on the bowel. Apparently when a wave approaches one of the scar-tissue barriers it pulls on the muscle on the other side; it stretches that muscle and thereby produces a contraction.

There is yet another way in which waves may spread from fiber to fiber or across connective-tissue barriers, and that is by means of the *electric action-currents*. It is well known that

when a muscle contracts or a nerve conducts, a small and transitory current is formed. This always runs in a circuit from the active place through the tissue to the resting place and back again through the surrounding medium. It has long been suspected that these action currents might lead to a progression of activity by stimulating the tissue just beyond the active place; and in recent years, largely through the efforts of R. S. Lillie, that view has become strengthened almost to a certainty. Two of his interesting observations are worth quoting at this point. If one of the combs of a Ctenophore is cut off and left for a while in sea water, it curls up so that the two ends are brought within a few millimeters of each other. It frequently happens then that the wave of ciliary motion jumps the gap between the ends and goes on, so that a wave of activity runs around the ring for hours at a time. Similarly, if a large number of spermatozoa of the annelid Nereis are allowed to stand in a watch crystal they tend to form layers and to contract rhythmically in unison. With the waves of activity going back and forth they give the picture of a layer of ciliated epithelium (Lillie, 1914, p. 428). In these two experiments there can be little question as to the mode of transmission across the liquid medium; and certainly nerves have nothing to do with it. According to Wyman they do not seem to have anything to do with the conduction of the stimulus from cilium to cilium in the mucous membrane of some of the lower forms of life.

All this emphasis has been placed on non-nervous types of transmission, not because I think the nerves are without function or that they do not ordinarily expedite conduction, but because I wish to show that peristaltic or wave-like movements can take place along gradients without the help of especially designed nervous mechanisms.

What is a Gradient? Perhaps at this point it might be well to stop for a moment to discuss what is meant by the term gradient, because the reader who does not now grasp its exact significance will not get much out of the next few chapters. The only men who seem to be really conversant with that term are the physicists and the engineers, and for that reason I always find it a pleasure to talk to them about

the gradient theory of peristalsis. They not only grasp the idea instantly, but they are also disposed to accept it; they are so accustomed to studying the flow of liquids along gradients of gravity or pumping pressure, of electricity along gradients of potential, or of the winds along gradients of barometric pressure, that when they see material being carried through a muscular tube, nothing is more natural for them than to think of a gradient of pressure or force.

A gradient is a gradation, usually in some attribute or state or force or activity, which is to be found between certain limits in space or time. Thus, it is not enough to say that there is a gradient or gradation of temperature; one must add that it is between, let us say, the inner and outer walls of an incubator or between the two ends of a metal rod. Similarly, in discussing the upward gradient in the pitch of a siren's shriek, one must say that it extends between two points in time such as the moment when the steam is turned on and the moment when the wheel reaches its highest speed.

Hence the use of the term "gradient of the digestive tract" should be avoided because it is too vague. As will be seen later, one really should specify the gradient either of rhythmicity, of tone, or of carbon dioxid production, between the cardia and the incisura, or between the pylorus and the ileocecal sphincter. In many places in this book I fear that I have used the term gradient or gradients rather loosely myself, but that is due largely to a desire to avoid a lengthy statement to the effect that there are probably a number of gradients, all related, all serving to direct peristalsis caudad, and all based on some fundamental gradation in the structure or in the metabolic rate of the contractile tissues. When we know exactly what that is we shall have at our disposal a short and useful term; in the meantime, for the sake of brevity, we sometimes have to say "gradients."

Another point that must never be forgotten is that a gradient is not a tangible thing which can be raised or stimulated or depressed or laid hold of directly. It is only an expression of relationship. Thus, the gradient of a railroad is the degree of inclination of the track as it spreads mile by mile over its territory; it can be represented by a graph in which

heights above sea level are plotted as ordinates and distances from some starting point as abscissas. In my experience, the trouble with the average student is that he either takes the plotted line for the gradient, or worse yet, he thinks that the roadbed is the gradient. If he is ever to think and talk clearly about the subject he must remember that the only way in which he can alter the gradient is by raising or lowering the height of some part or parts of the roadbed.

At first thought these points may not seem worthy of so much insistence, but we must always remember that there can be no interchange of scientific thought unless technical terms are used precisely and always with the same meaning. It is necessary also to keep in mind what a gradient is for, or what it can possibly do. So far as I know, all that the basic gradient can do is to make it easier for waves to travel in one direction than in the other. Similarly the gradient of a railroad makes it easier for trains to run in one direction than in the other, and one does not question the existence and significance of that gradient simply because it does not also run the telegraph office. Again, I may seem to be uttering needless warnings, but the experience of the last few years has shown me that many men, for want of a clear understanding of just what a gradient means, first ascribe to it duties which it cannot possibly assume, and then express disappointment because it does not come up to their expectations.

The Gradient in the Heart. Returning to the simile of waves spreading in water, it seems to me that some tubular organs may be likened to ponds which are level to begin with while others are more like rivers which have definitely established gradients. In the first case, the waves spread equally well in all directions; in the second, the waves spread more easily downstream than up. Perhaps I can illustrate this point best by showing the evolution of the fixed *gradient in the heart.* As is well known, in that organ the beat follows a gradient of rhythmicity from the sinus to the ventricle. It was Gaskell (1883) who first pointed out that "the rhythmical power of each segment of the heart varies inversely as its distance from the sinus."

Thus, if we cut a heart into three or four pieces, the one containing the mouths of the great veins will show the greatest tendency to beat rhythmically, and it will have the fastest rate; the ventricle will be slow to start beating and it will have a slow rate. If, however, we turn to the primitive heart of the sea slug, Aplysia, we find a tube which apparently has no constant gradient in either direction. Its beat arises now on one side and now on the other, depending on where the blood produces the greatest tension (Straub, 1901, p. 518). Hunter could find no sign of a gradient in the heart of one of the ascidians. In these animals the beat runs for a while towards the viscera and then for a while towards the gills. The pacemaking end seems to get fatigued; its rate is slowed and finally the other end is able to assume the pace for a while. A constant direction of contraction may be maintained by electrical stimulation of either end of such a heart (Bancroft and Esterly). It seems to me that Hecht's studies on Ascidia atra show us the very beginning of the fixed gradient which we find in the hearts of the higher animals. He found that although the heart of the ascidian reverses its beat from time to time, the sum of the advisceral beats is about twice that of the abvisceral. Moreover, as we should expect, if the gradient is a little better in the advisceral direction, the rate of conduction is definitely faster in that direction than in the other. If a wave is started in the middle of the heart, going both ways, it tends to efface the abvisceral waves, which according to our theory would have the smaller momentum. It is interesting also that under slightly adverse conditions, as after warming the water, or after diluting or concentrating it, it is the abvisceral beat which is suppressed.

Other interesting observations have been made by Gerould on the heart of the chrysalis of Colias. In the earlier stages of caterpillar existence, the heart beats in an orad direction. Later there are alternating periods in which the heart beats either backward, forward, or both ways from the third and fourth abdominal segments. As the chrysalis develops, the periods during which the heart beats forward become longer and longer, and as one would expect if a gradient were

developing, the rate of the backward beats, against this supposed gradient, is about one-half of that of the beats which run forward with it.

We find a little more stable but still reversible heart beat in the sharks and rays (Bottazzi, 1902[b], p. 372; Gaskell, 1900, p. 184). In them, the slightest stimulus to the bulbus aortae will reverse the beat and the same stimulus to the sinus will restore it. Even in the higher vertebrates the heart beat can be reversed temporarily by agencies which lower the rhythmicity of the auricle or raise that of the ventricle (Eyster and Meek). Ordinarily, however, as we have seen, the beat arises in the sinus region and keeps coming from there because that area has the greatest rhythmicity and the fastest inherent rate.

Gradients in Other Organs. There is considerable evidence now that peristalsis in the ureter follows a gradient of rhythmicity from the kidney to the bladder (Penfield, Lucas, Sokoloff and Luchsinger, Satani, Wislocki and O'Connor, Hryntschak, Graves and Davidoff, and Gruber, 1927). I have done some work with excised segments of ureter and have found that the rate of rhythmic contraction is often fastest in the piece removed from the kidney end. This gradient, however, is not so constant or so marked as it is in the bowel. I have records also from segments of the fallopian tube and vas deferens which suggest that there are similar rhythmic gradients in those tubes.

We may perhaps later be able to state it as a general physiologic law that the direction of transport of material in a tubular organ depends on gradients of rhythmicity, tone and irritability. When we come to think of it, our experience with engineering and physics should have led us long ago to look for gradients in these muscular tubes. We know that water in a pipe follows gradients of gravity or of pumping pressure; electricity flows along gradients of electromotive force, the winds follow gradients of barometric pressure, and so forth. Moreover, anyone who has ever tried to milk a cow knows that it is not hard squeezing which brings results, but a coördinated, graded contraction beginning at the top of the teat and working down to the end.

The Gradient in the Rate of Rhythmic Contraction in the Intestine. What evidence have we now that there is a gradient in the gastrointestinal tract? So far as rhythmicity goes the evidence is overwhelming. It is a simple thing to open a rabbit under salt solution and to demonstrate that the rate of rhythmic contraction varies from about twenty per

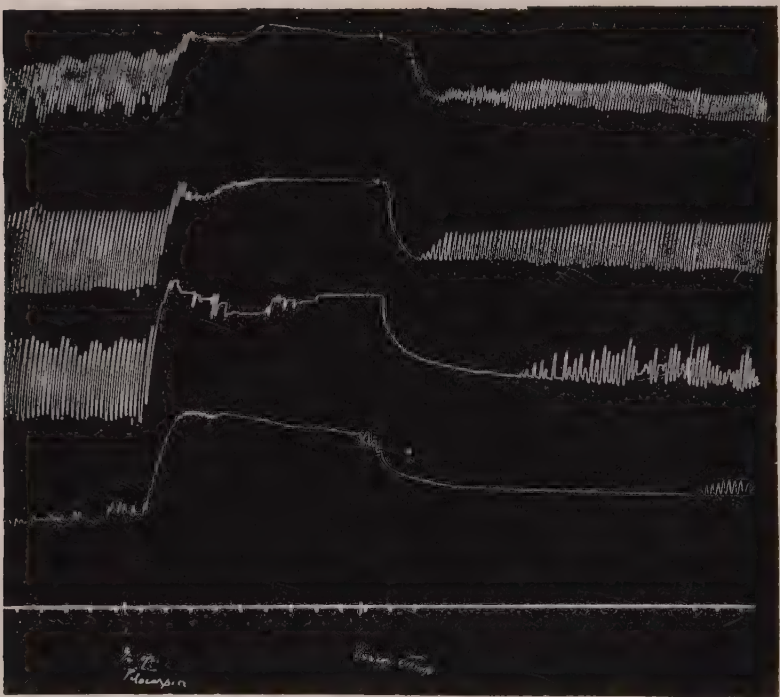

Fig. 16. To show the difference in the rate of rhythmic contraction in excised segments. Note also the graded recovery from pilocarpin after adding atropin. From above downward, the records are from duodenum, upper ileum, lower ileum and colon. Time record represents thirty seconds.

minute in the duodenum to ten per minute in the lower ileum (Alvarez, 1915[a]). It is easy also to cut out short segments of the bowel and to show that their rate of rhythmic contraction continues to vary inversely as the distance from the pylorus (Alvarez, 1914, and 1918[a]).

A similar gradient can be shown in strips of muscle excised

from the wall of the stomach (Alvarez, 1916[a]). There the fastest rate is found in the strip from the lesser curvature near the cardia. It is harder to show the gradient in the colon (Alvarez and Starkweather, 1918[c]) but that is to be expected when we remember that the large bowel is more sluggish than the small; it lets the contents lie in one place for long periods of time and it often shows reverse peristalsis. Hence it is that the excised piece is slow to start beating; its rate is slow; it tends to contract down into a hard knot and stay that way, and the gradient is poor and often reversed. In the small intestine of the rabbit and the white rat the rhythmic gradient is so fixed and so intimately "built into" the structure of the intestine that in healthy animals one can determine the oral and aboral ends of short excised segments by counting the rates at the two ends.

Reversal Experiments. It has always seemed to me that the gradient is more stable in the rabbit, guinea pig and rat than in the cat and dog, perhaps because the first three have long thin intestines and bulky food, while the last two have short, strong-walled ones and more concentrated food. As will be seen shortly, the gradient must be well established if rough solid particles of food are to be passed on. If we think of the bowel as a pipe line with uphill stretches in it, we know that water can be forced through such stretches, but not rocks. Similarly, if we take dogs, cut out sections of their small intestines, turn them end for end and anastomose them again, we can keep the animals alive for months if the greatest care is taken to keep rough and indigestible foods from them. Eventually they die from intestinal obstruction, and autopsy shows that bits of straw, bone, wood, etc., have accumulated at the upper suture and have finally blocked the lumen (Kirstein, Mall, 1896[c], p. 93, Kelling, 1900, Mühsam, Enderlen and Hess, Prutz and Ellinger, 1902 and 1904, Ellinger and Prutz, Beer and Eggers, McClure and Derge, Cannon, 1911[a], p. 142, Edmunds and Ballance, Glassner, and Segale, 1921). (See Fig. 17.) It is clear that the original direction of peristalsis remains fixed in these loops, and that liquids can be forced through when solids cannot. Segale, who studied some of the animals with

the roentgen ray, found that gas also cannot always be forced through the reversed loops.

Liquids can be pumped into the rectum of a cat or dog until they flow out of the mouth, but Bayliss and Starling (1899, p. 106) found that any attempt to force a solid body like a tampon on a stick in the orad direction through a

FIG. 17. Shows the results of reversing a segment of dog's intestine. Note enormous spindle-shaped dilatation on either side of the upper anastomosis. *A*. The point of greatest dilatation is 3 cm. above the suture, on the normally directed intestine. Lower anastomosis of reversed loop is at *B*, where lumen remains of normal size. (*From McClure and Derge.*)

loop of living bowel was likely to result in tearing on account of the resistance developed.

THE FUNDAMENTAL NATURE OF THE GRADIENT. The results of the reversal experiments make me feel that the basic gradient in an organ must be fundamental and built in from the beginning, and not, as some might think, the result of functional adaptation. In order, however, to make more certain of this point, I looked for and found a gradient of catalase content along the small intestine of the fetus of

the pig; and recently, Murray has, I think, clinched the matter by showing that fragments of auricular muscle taken from chick embryos and grown in tissue cultures beat from two to six times faster than do similar fragments taken from the ventricles.

The permanence of the gradient in the gut is to be expected also from studies on the lower forms of life. The mouth of a frog is lined by epithelium covered with little cilia which wave in one direction. If a piece of this epithelium is cut out, turned through an angle of 180°, and grafted back again, the cilia continue to beat in their original direction, now contrary to that in the rest of the mouth (von Brucke 1916). In some of the worms the so-called "polarization" is so perfect that if the animal is cut into many small pieces they will all crawl in the same direction toward the point where the head used to be (Carlson, 1904, p. 284; Biedermann, 1906, p. 288). The early development and stability of these gradients of growth and activity are well shown by some experiments resembling those in which the segments of intestine were reversed. Hooker chiseled out little segments from the cervical region of the growing spinal cord of frog embryos; he turned these pieces end for end, and grafted them back into place. The interesting thing is that the nerve fibers in the reversed segment continued to grow in the original direction in spite of the great force which was exerted against them by the growth of fibers coming down from above. A similar reversal of segments from the duodenal region of tadpoles produces situs inversus in the abdominal organs (Pressler).

SUMMARY

Waves tend to spread out in both directions from a stimulated place on a muscular tube much as ripples spread in a pond when a stone is thrown in. If the stone is thrown into a river the waves will travel downstream more easily than up. Similarly in the heart and intestine, a gradation in rhythmicity makes it easier for the waves to go in one direction than in the other. Actually, in the bowel, Miss Starkweather and I found that the effect of a stimulus could be detected much farther caudad than cephalad (1919).

CHAPTER VIII

THE UNDERLYING METABOLIC GRADIENT

We have seen that there is a rhythmic gradient in the bowel from the pylorus to the colon. The next question is: What is there underlying this gradient; how did it come, and how is it kept up? Should we not expect to find *anatomic* and *metabolic* gradients running parallel to the rhythmic one? Those who are partial to theories of neurogenic origin will probably think first of looking for some graded difference in the structure of Auerbach's plexus; and actually such a difference has been found. Gerlach showed years ago that the mesh of the plexus becomes coarser and the ganglion cells fewer as one goes from the duodenum to the ileum; and more recently, Kuntz (1918) has found a gradient in the concentration of the sympathetic neurones, from the duodenum to a point about 12 cm. above the ileocecal sphincter. It seems to me, however, that as the evidence summarized in Chapter II points to the myogenic origin of the rhythmic movements, we must not rest satisfied with these findings but must look also for graded differences in the structure and chemical activity of the muscle.

Rate of Contraction Varies with Metabolic Rate. Now, it has been shown that the rate of rhythmic contraction of a muscle is dependent upon the rate at which its *chemical processes* go on. Some substance seems to be built up to a certain point and then perhaps exploded or torn down to produce the contraction; if the metabolic rate is slow it should take longer to complete the cycle. As Woodworth says, the rate of contraction seems to be adapted to the metabolism of a muscle; "if the pause preceding . . . is too short, the contraction suffers from lack of recuperation. If it is too long, the contraction suffers from what we may perhaps call a sort of drowsiness." We know also that warming hastens chemical processes, and Magnus (1904[a]) and Taylor and Alvarez have shown that warming the intestine hastens the rate of rhythmic contraction. As we can take a piece

of ileum beating 10 times a minute and by warming it, speed up its metabolism so that it will beat 17 times a minute, it seems to me that the duodenum which normally beats 17 times a minute probably has a faster metabolic rate than the ileum.

The warming not only increases the rate of contraction, but it shortens the latent period and markedly alters the form of the contraction curve. These changes probably account for de Zilwa's finding that with a muscle at 40°c., stimuli have to follow each other at intervals of from four to ten seconds if summation is to be obtained. At 25°c. the interval can be twenty seconds or more. Similarly Englemann while studying the ureter of the rabbit, found that a series of subliminal stimuli might bring about a contraction if the interval between them was not too great for summation. When the irritability was high and the waves were traveling rapidly down the ureter, the interval had to be shorter. It had to be shorter also when using the ureter of the rat, as there the rate of the waves is normally faster than in the rabbit. It seems clear, then, that a muscle which beats 17 times a minute is different from one which beats 10 times a minute. It apparently has been constructed differently in some way, so that its chemical processes will go on at a faster rate, much as those of a baby go on faster than those of an adult. Those who would like to learn more about this relation between activity and metabolic rate should turn to an interesting article by Miss Hyman (1919[d]). As she (Hyman, 1919[b], p. 378) points out, the word *metabolism* is generally taken to signify the sum of all the energy-producing and substance-producing processes occurring in the body; but as the oxidative processes are the most important ones it is sufficient for our purposes to measure the rate of respiratory exchange. Child (1920, p. 152) uses the word *metabolic* gradient, not because he is satisfied that it is purely or primarily metabolic in character, but because oxidation seems to be the "fundamental factor in life and the chief source of the energy of living organisms . . . Protoplasm is a system in which the chemical reactions of metabolism are so intimately associated with other factors, *e.g.*, colloid dis-

persion, active mass of enzymes, permeability of limiting surfaces, electrolyte and water content, etc., that to attempt to distinguish one particular factor . . . as primary is at present impossible. The term 'metabolic gradient' . . . means only that the metabolic factor is a characteristic feature . . . The term 'physiologic gradient' which avoids all specific implications might be substituted for it."

Reasoning along these lines, Miss Starkweather and I (1918[a]) measured the CO_2 production of equal weights of muscle from different parts of the bowel and found a definite gradation from the duodenum to the colon. With the help of F. B. Taylor, we obtained some evidence also of a gradation in the amount of oxygen used by equal weights of muscle from the different regions, and Evans (1923) has since shown this with the microcalorimeter. Using muscle from the cat, he obtained the following figures: the duodenum uses 0.45 c.c. per gram per hour, the middle jejunum uses 0.31 c.c. and the lower ileum uses 0.29 c.c. Unfortunately, he does not say whether or not the muscle was contracting. If it was, the oxygen intake in the upper part of the bowel could be higher, simply because the muscle was contracting more actively. Actually, I think the duodenal muscle contracts more actively because its metabolic processes are more active than those of the muscle in the ileum, just as the child is more active than the adult for the reason that its basic metabolic rate is higher.

To throw light on the foregoing point, Miss Starkweather kept segments of intestinal muscle paralyzed with epinephrin and was still able to show the gradient of carbon dioxid production. Still more satisfactory evidence that the metabolic gradient is basic and built into the muscle from the start has recently been obtained by Howard and Sollmann. They used segments from different parts of the turtle's heart, and kept them quiet by immersing them in an isotonic solution of a non-electrolyte, sucrose, which had no damaging effects. On putting these segments into a modified Osterhout microcalorimeter they were able to demonstrate a clear-cut metabolic gradient, running from the sinus-atrium to the

base of the ventricle, then to the apex of the ventricle and lastly to the sinus-free auricle.

Miss Starkweather and I found graded differences also in the catalase content of equal weights of minced intestinal muscle. These differences were suggestive because there are many reasons for believing that catalase is involved in some way in the normal oxidative processes of the cell; just how

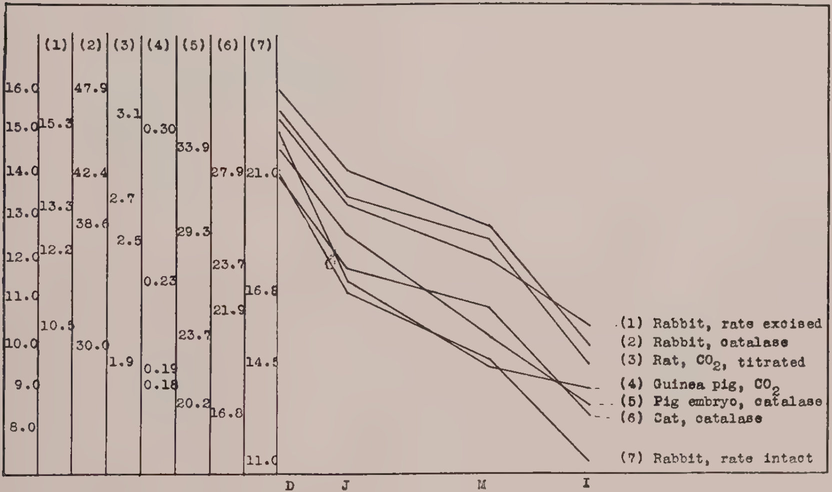

FIG. 18. Showing the parallelism between the gradients of rhythmic contraction, CO_2 production, and catalase content in different animals. In order to bring the different curves closer together, an arbitrary set of ordinates was chosen running from 8 to 16. The seven sets of data were then multiplied or divided by factors which would place the first figure for the duodenum between 14 and 16. The original data are shown as ordinates in the seven columns on the left. The numbered columns correspond to the numbered legends identifying the different curves. The abscissas represent the four segments along the gut.

we do not know. Since Miss Starkweather and I worked on this problem, many papers have appeared which have shown that there are several pitfalls for the worker who uses a poorly controlled method, but I think we avoided them by making the determinations for one animal all at the same time, in the same shaking machine, at the same temperature, and with the same neutralized hydrogen peroxid.

It turns out, also, that we were fortunate in using for our readings amounts of oxygen liberated after a given time because Northrop has since shown that they are directly proportional to the concentration of the catalase. Actually, in our experiments, it was remarkable how closely the gradient of catalase content paralleled the gradient in the rate of rhythmic contraction. This can be seen in Figure 18.

Significance of the Findings. To my mind the important point is not that these catalase determinations indicate the presence of a metabolic gradient; that has been shown with more direct and more certain methods. The important point is that there is a striking and undoubted gradation in the distribution of some chemical substance along the length of the bowel. More such gradients will, I feel sure, be found when they are looked for. As an example, there is the striking gradient in the lactic acid content of resting muscles from different levels of the small bowel found recently by Evans (1925), and the gradient in susceptibility of the rhythmic contractions to the presence of calcium, shown by Robertson in the intestine of the fly. Other forms of chemical analysis would probably show differences in composition similar to those found by Lee, Guenther, and Meleney when they compared the diaphragm with other skeletal muscles. Most interesting and suggestive is Murray's finding that the rate of metabolism in chick embryos decreases with age, and that associated with this gradient, are gradients in the pH of the tissue juices and in the concentrations of chlorids, carbonic acid, and protein.

Axial Gradients. Gradients in metabolic rate have been shown to exist in many parts of the body and it seems to me that their importance in biologic studies is going to be realized more and more as time goes on. They appear at the very begining of life in the ovum and thereafter have much to do in controlling the development of the organism. Thus in the frog, that part of the egg which happens to get the best blood supply from the ovarian membrane forms the embryo (Bellamy). The most rapidly growing part of the embryo forms the nervous system; and the most rapidly growing part of the nervous system becomes the brain. These differ-

ences in metabolic rate show themselves as differences in the rate of cell division and in the size of the cells along the future axes of the organism. They are found not only in ova, but in developing seeds, where the polarity is often determined by slight differences in illumination (Child, 1920, p. 170).

Once such regions of rapid growth are established, their activity serves to regulate and hold in check the growth of other parts of the developing animal or plant. This control can easily be demonstrated by cutting off or impairing the growth of the tip of an evergreen tree or the head of a primitive type of animal like a hydroid or a planarian worm. In the simplest organisms there is only the apico-basal pattern with its corresponding gradient, but in higher forms with lateral symmetry there are radial gradients running at right angles to the longitudinal or polar ones (Child, 1920). Thus in certain algae and in trees there is a metabolic gradient along the main trunk from the rapidly growing tip to the roots and there are other gradients in the branches from the tips to the trunk. It is a remarkable thing that in some plants and lower animals these original gradients can be effaced, altered or reversed either accidentally or experimentally; and with the change in gradient goes a change in the structure of the animal. Thus a piece of a planarian worm may develop a new head where the tail used to be; or the experimental obliteration of the polar gradient may cause the new individual to develop along the original gradient of lateral symmetry, with a head on one side and a tail on the other. Just as slight accidental advantages in oxygen supply, illumination, or other conditions which favor growth determine the location of the animal pole of the egg, so they may enable some group of cells to seize control and to rearrange an adult organism along new axes (Child, 1920, pp. 158, 172).

Gradients in Electrical Potential. Although there is still considerable doubt as to the exact mechanism of this control, more and more evidence is accumulating to show the importance of the minute *electric currents* which are produced in these metabolic gradients. If we put two pieces of metal of different composition into a solution of some elec-

trolyte and connect them to a galvanometer, we find a current flowing between them. If the electrodes are chemically the same but the concentration of the electrolyte about them is different, a current will again be set up. In the tissue there are no metal electrodes and no wires; but differences in ionic concentration on the two sides of cell membranes and differences in the rates of oxidation along growing axes give rise to circuits through the tissues themselves (Lillie, 1917). If two regions with different oxidative rates are connected through wires to a galvanometer, the more actively growing or more motile one is always electronegative to the other; that is, the current flows towards it in the wire. In the tissue, of course, the current flows from the more active end of the metabolic gradient to the less active end. Similarly, in a battery, the zinc *plate* is positive to the copper, although the copper *terminal* is positive through the galvanometer to the zinc terminal.

Years ago Hermann noticed that the growing root tips of seedlings were negative to the other parts of the root. Müller-Hettlingen confirmed this and showed, moreover, that the growing tip of the plant was negative to all other regions. Later, in 1902, Mathews found that the head of a polyp was electronegative to the stem, and anterior levels of the stem negative to posterior ones; and in recent years Child and his students have found gradients of electric potential along all the axiate animals and plants which they have studied (Child, 1920).

We are just beginning to see that these minute differences in electric potential can play a large part in the development and life of the organism. They not only bring about certain chemical reactions which otherwise would not take place, but they direct them along certain lines. One of the simplest and best known examples of the "chemical action at a distance" is found in the electric battery where two pieces of zinc and copper form the electrodes and dilute sulphuric acid serves as the electrolyte. Very little chemical action takes place until the two pieces of metal are connected by a wire, but immediately after that the zinc begins to be eaten away. Many other interesting examples of this action might be

supplied, and if space permitted I might review the work of Lillie (1917) and others who have used weak electric currents to build beautiful structures closely resembling corals, seaweeds, trees, toadstools, etc. Years ago Mathews suggested that in lower animals we might be able to modify and control at will the regeneration of lost parts by modifying the bio-electric currents, and recently Lund (1921, 1924) and Ingvar have shown that such control is possible. Lund was able to determine the point of regeneration in Obelia; and Ingvar caused the cell bundles in tissue cultures to grow along the lines of force produced electrically in his tissue cultures. He found, moreover, that he could produce these effects with currents comparable in intensity with those found in living tissues.

In addition to the axial gradients of growth there are other metabolic gradients in various organs. As was to be expected from the character of the electrical phenomena, there is a metabolic gradient in the embryonic heart of the chick from the sinus to the ventricle (Child, 120, p. 169; Howard and Sollmann). MacArthur and Jones found a gradation in respiratory rate in the nervous system from the cerebrum to the peripheral nerves, and Tashiro has demonstrated gradients of CO_2 production along nerves. He believes that these gradients which are from the center to the periphery in motor roots and from the periphery to the center in sensory roots have something to do with the conduction of impulses.

That the botanists are becoming interested in gradients is shown by papers like that of Gustafson on gradations in the hydrogen-ion concentration of the juices along the main axis of stems and leaves, and that of Hurd-Karrer on gradations in the osmotic pressure and specific gravity of the sap from the base to the tip of the cornstalk.

This long digression into fields distant from that of the intestine has been made in order to show the growing importance in every department of biology of a new idea. It will undoubtedly be a long time before research workers are in agreement as to the exact significance of these gradients, but, as Child says, there can be no doubt about their existence. They are there, and the natural inference is that they must be useful or at least worth studying.

CHAPTER IX

OTHER RELATED GRADIENTS

A Gradient of Force. Several years ago while working with a man who had a jejunal fistula I found a marked difference in the *pulling force* exerted by different parts of the bowel on balloons. The jejunum pulled almost constantly and with considerable strength, while the ileum pulled intermittently and weakly. Searching through the literature I found that Hess had observed the same thing in dogs with gastric fistulae through which he could insert balloons into the duodenum. Eighteen centimeters from the pylorus the pull corresponded to 228 gm.; 20 cm. farther down it was 90 gm.; and 12 cm. farther below that, it was 75 gm. Later, Brandl and Tappeiner worked out the rest of the gradient farther down the ileum.

Their figures run as follows:

Centimeters from the pylorus..	115	125	135	145	155
Pull in grams................	32.6	31.8	28.0	21.8	17.5

It would seem clear from these experiments that there must be a gradient of propulsive force along the bowel much like that in a pipe line.

Latent Period. When a muscle is stimulated it does not respond immediately. There is a short, so-called latent period the length of which depends largely on the metabolic rate of the muscle. As the metabolic rate has been shown to vary in different parts of the gut, we should expect the latent period to vary, and actually it can be shown that it does. As will be seen in the next chapter, it is quite easy to show a gradient of latent period in the stomach. In the bowel the technical difficulties are much greater, and it is almost impossible to get satisfactory measurements with some animals. In many others, however, I have been able to show a definite gradation from a short latent period in the lower duodenum or upper jejunum to a long one in the ileum. Figure 19 shows data obtained with dogs. The first portion of the duodenum generally reacted poorly and after a

fairly long latent period. That may be due at least in part to its relatively greater susceptibility to the trauma of excision and handling, and in this connection it is of interest to note in the paper of Howard and Sollmann on the metabolic gradient in the heart, how rapidly the chemical activity of the strip from the sinus declined as compared with the other, less sensitive, segments.

While studying these latent periods and the shapes of the contraction curves, I could not help being greatly impressed

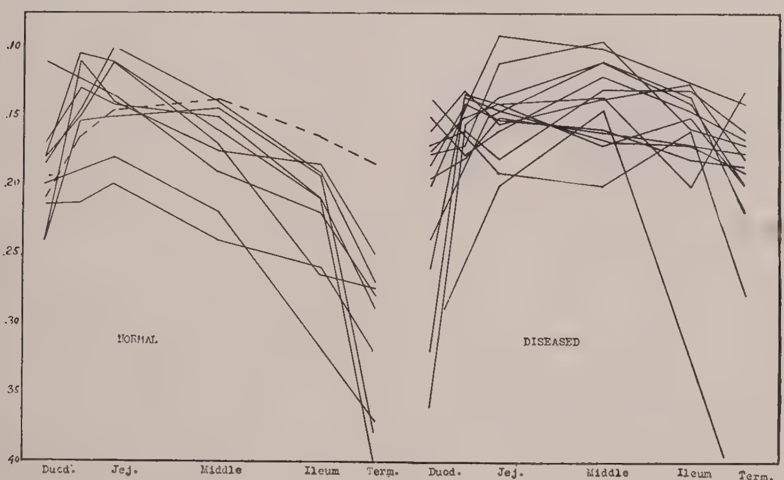

FIG. 19. Shows gradation in the latent period of the dog's small intestine. The ordinates represent parts of a second; the abscissas, distances from the pylorus. The data shown at the right were secured from distempered or otherwise diseased dogs.

with the marked differences which exist between the muscle in different parts of the stomach, small bowel and colon.

TONE. When a piece of duodenum or jejunum is cut out it tends to contract down to perhaps half of its original length and the ends roll over so as to form little cuffs. A piece of ileum may even lengthen a little, and its cuffs, if any form at all, are narrow as compared with those of the upper bowel. I found recently that these little cuffs with their differences in width were described in 1902 by a medical

student (Wolff). Similar differences in the tone of the muscle from different parts of the stomach are described in the next chapter. When a loop of bowel is full of food and actively segmenting it is generally contracted tonically. Later, when it empties, it may relax and more than double in length (Alvarez, 1915[a]; Mall, 1896[b]). These permanent and transitory differences in tone are undoubtedly of great importance in digestion, and should be studied further. As Cannon, 1908, p. 27, also 1911[a], p. 195, and 1911[c], p. 242, and 1911[b], p. 417) has shown, they have much to do with initiating and regulating peristalsis in all parts of the digestive tract. He was able to reverse the direction of peristalsis in a loop of intestine by dipping the caudad end into a weak solution of $BaCl_2$ (Cannon, 1912, p. 119). As is well known, that raises the tone of the muscle. In the crop of the sea slug (von Brücke, 1916) and in the earthworm (Biedermann, 1906, p. 483) it has been shown that the contractions start from the place of greatest tension; changing that, the direction of peristalsis can be reversed at will. Trendelenburg (1917[a]) has observed the tendency of a loop of guinea-pig intestine to contract more at the cephalad end than at the caudad, and has suggested that this gradient of tone accounts for the direction of peristalsis.

Rhythmic Tendency. When a number of segments from different parts of the rabbit's intestine are placed in a beaker of warm oxygenated Locke's solution, the duodenal segment is generally the first to begin beating, and the colon is generally the last. Figure 16 shows also that when a number of beating segments are thrown into spasm by pilocarpin and then released again by atropin, there may be a remarkable gradation shown in the tendency to resume rhythmic activity. Conditions in the intestine are very similar, therefore, to those in the heart where the excised auricle can be made to beat easily, but the ventricle only with difficulty. If this tendency is as marked in the intact animal as it is in the excised segments, its usefulness is obvious. It will conduce to the starting up of normally directed peristalsis after the bowel has been paralyzed by poisons or by powerful splanchnic inhibition.

Irritability. As stated in the preface, the first gradient which I noticed was one of irritability; I found that the duodenum was more responsive to distention by gases or food than was the ileum. Later, while working on men and women with intestinal fistulae I found that a balloon in the jejunum was kneaded and pulled on almost incessantly; in the ileum, it was often left undisturbed for a half hour or more, and in the colon it was left entirely alone except for an occasional contraction immediately after it was distended. A search through the literature showed that others have made similar observations. Van Braam Houckgeest, Flöel, Schillbach (p. 281), Bokai (1887[b]), Biedermann (1889, pp. 372 and 379), Lüderitz (1889 and 1890), and Bayliss and Starling (1899), all commented on the greater activity and responsiveness of the duodenum and jejunum, and the last-named writers thought that "ascending augmentor stimuli" and the "higher excitability of the duodenal end of the gut" might perhaps have something to do with the preponderance of downward peristalsis. Schillbach used faradic stimuli so weak that they had practically no effect on the bowel except in the upper jejunum and upper end of the colon. Similar results were obtained by Biedermann with the galvanic current. He thought the irritability was graded downwards and that there must be a histologic gradient perhaps in the structure of Auerbach's plexus. He tried to prove this pharmacologically much as I tried in 1913.

It is easy to show the gradient of irritability in the bowel with distending balloons, pinches, and salt crystals, but it is not easy to show it with the electric current. I have tried many times to work out a satisfactory technic but have never been able to convince myself that the threshold for the duodenum is less than that for the ileum. The rhythmic changes constantly going on in the intestinal muscle and the prolonged refractory periods make such experiments unsatisfactory and inconclusive. There seems little doubt that the chemical threshold is the same in different parts of the gut; that is, five segments from different regions, if they are all beating strongly, will respond equally to minute dosages of drugs like barium chloride or pilocarpin.

Marked differences in irritability were found in different parts of the wall of the stomach, but those will be discussed in the next chapter.

King and Arnold (1922) found a graded difference in the response of the mucous membrane of the small intestine to splanchnic stimulation. It was "sharpest in the duodenum, good in the jejunum, and almost negative in the ileum."

Early Observations on the Rhythmic Gradient. This book would not be complete without references to the work of previous writers on the subject. When in 1913 I started studying the differences in rhythmic rate which appeared on my tracings from two different parts of the bowel, Dr. Cannon told me that he had noticed such differences but he had never had time to analyze them, and so far as he could remember, he had never read anything about them. During the next year a search was made through the literature, and little was found that would lead anyone to suspect that the neuromuscular tube of the small intestine is any different in the duodenum from what it is in the ileum. Even Roith, who had the vision to see that the peculiarities of colonic activity might be due to regional differences in muscle and tone, states that the small intestine is the same throughout. After long search, however, I found references to differences in rhythmicity in Luciani's "Textbook of Physiology," and in articles by Legros and Onimus, Lüderitz (1890), and Laqueur. Legros and Onimus thought that the emptiness of the jejunum was probably due to its fast rate. Nothnagel remarked upon the fact that in the rabbit the movements of the upper bowel are stronger and more continuous than those of the lower. Stiles noticed a rhythmic gradient along the esophagus of the frog; and Bottazzi (1898, and 1902[a], p. 341) ascribed the aboral course of the waves in the esophagus of the sea slug Aplysia to the greater tone and excitability of the oral region in which they arise. He suspected a difference in rate, but he could not show it. Bottazzi deserves much credit because he knew what he was looking for and the value of what he found in the esophagus. I cannot tell from their papers whether the later writers knew of the work of Legros and Onimus. Pohl knew of Lüderitz's work, and Luci-

ani may have derived his knowledge from the same source. As was shown in the preceding section, a number of the older writers observed the gradient in irritability. Hess, and Brandl and Tappeiner noticed the gradient in pushing force down the bowel, described in Chapter IX.

Unfortunately, these men did not realize the value of what they had found; they did not have the present-day background to fit it into, and they did not keep hammering away on the subject until they had compelled their confrères to listen. We may sometimes regret the fact that textbooks are sluggish and conservative things, but when we remember that it often takes from fifty to a hundred years to purge them of some misquotation or false conclusion, we should perhaps be glad that it takes ordinarily from ten to twenty years of reiteration to get a new idea included. To my mind, the main cause for the slow development of our knowledge of the mechanics of peristalsis is to be found in the fact that most of the men who worked on the bowel were so concerned with problems of nerve supply or drug action that they made mention of important physiological observations only in passing. A striking illustration of this is found in Jacobj's (1890) description of reverse peristalsis in the colon which was buried away and lost in an article on colchicum poisoning until some time after Cannon's independent discovery of the same phenomenon.

ANATOMIC STRUCTURE

The differences in the structure of Auerbach's plexus in different parts of the gut have already been mentioned (Gerlach and Kuntz, 1918). A gradation in the thickness of the muscular coat of the small intestine from the duodenum to a point a little way above the ileocecal sphincter has been described by a number of anatomists (Tourneux and Hermann, Flint, Merkel, Jonnesco, Kölliker, Monks, Schäfer, pp. 536 and 552, Todd, p. 145). Unfortunately, the normal transient differences in tone and the uncertain effects of the fixing agents make it hard to get trustworthy figures. These difficulties and the ways of meeting them are discussed in

Rost's article on the differences in the thickness and tone of the muscular wall in the colon of man.

One of the most interesting graded differences is the one pointed out so clearly by Monks, and Latarjet and Forgeot.

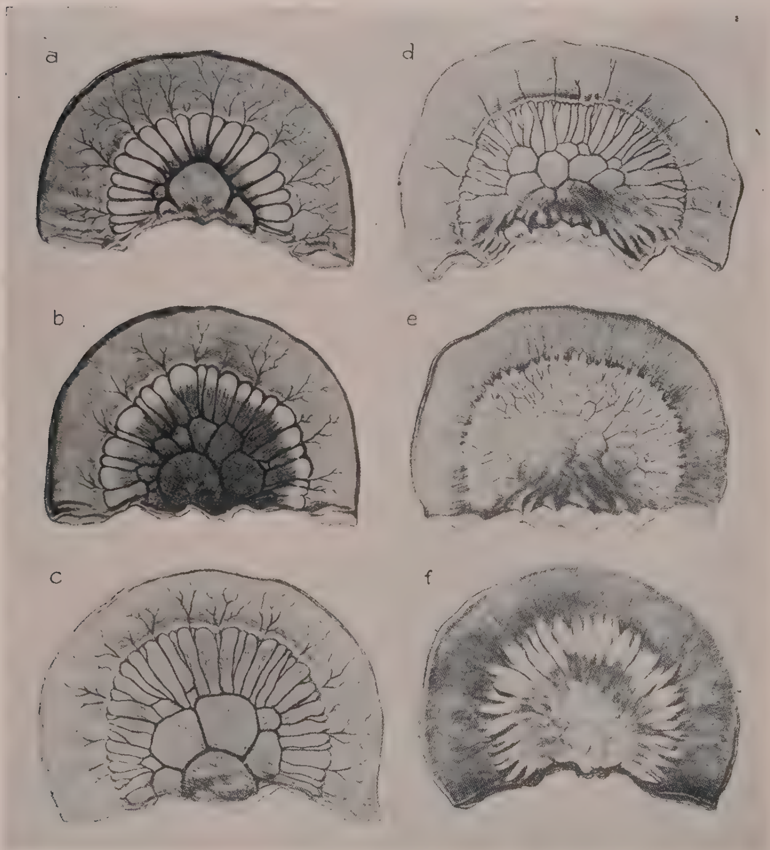

FIG. 20. Shows graded changes in the mesenteric arteries from the jejunum to the lower ileum in man. A, 3 feet from the end of the duodenum; B, 6 feet; C, 9 feet; D, 12 feet; E, 17 feet; F, 20 feet from the duodenum. (*From Monks, 1903.*)

They call attention to the fact that there is a progressive decrease in the vascularity of the mesentery from the duodenum to the ileum. Part of this difference in the mesenterial

arches is due to the greater functional activity of the mucous membrane in the jejunum, but part of it is due almost undoubtedly to the greater activity of the muscle. These observations fit in with those of Krogh who has shown that the blood supply to a muscle is an index of its metabolic rate. In keeping with its sluggishness and its low metabolic rate, the colon has a relatively poor blood supply; so poor that surgeons have to be very careful when making anastomoses with it.

CHAPTER X

CHEWING AND SWALLOWING; THE ESOPHAGUS

Especially in this era when it is so customary to sacrifice teeth it is well to remember that digestion begins in the mouth. Chemical action takes place largely on surfaces; so until the food is finely broken up and given an enormous surface area, there is little that the digestive ferments can do.

The amount of chewing that a particular mouthful gets depends partly on the dryness and toughness of the food, and partly on the subject's ability and willingness to swallow large masses. The average size of swallowed particles has been studied carefully by Fermi (1901[b]). Anyone who will take the trouble to examine a few stools will be surprised to see the size of the particles commonly swallowed. He will find parts of apple cores, intact peas and beans, cherry pits, and large pieces of orange, tomato, celery, lettuce, and other vegetables and fruits.

Strength of the Esophagus. It is strange that the carnivores do not seem to be endowed with any instinct to chew their food. Instead, they gulp down masses so large that one wonders sometimes how the esophagus is going to handle them. As one would expect, their gullets are supplied with muscles that are considerably more powerful than those of man. According to Schreiber (1911[a]) Mosso found that a dog could swallow a small ball of wood when, by means of a thread running out of a fistula and over a pulley, it was lifting 250 gm. At times the animal could lift 450 gm., but only through a short distance. Caballero, using a similar technic, obtained figures of from 150 to 200 gm. In human subjects Schreiber found that the esophagus could exert a pull of from 8 to 70 gm., the variations being dependent largely on the position of the balloon in the tube.

The herbivores cannot dispense with mastication, probably on account of the low digestibility of the seeds and grasses on which they live, and the need for cracking the little envelopes of bran which surround the food.

The Value of Saliva. The saliva serves to moisten the food so that it can be formed into boluses; it moistens the mucous membrane of the mouth, and lubricates the esophagus. As is well known, it serves to split some of the starch and to prepare the remainder for final digestion by the amylase of the pancreatic juice. As is pointed out in Chapter XIII, the absence of mixing movements and of much acidification of the contents in the fundus makes it possible for the ptyalin of the saliva to keep at work for some time after the food enters the stomach.

The Crushing Power of the Jaws. Black invented a little instrument with which he could measure the strength of the bite in man, and found that in most cases, the molars come together with a force of from 100 to 160 pounds. The corresponding figures for the incisors ranged ordinarily between 30 and 80 pounds. An athlete exerted a pressure of 165 pounds with his molars, and one subject, a physician who did not seem to be particularly athletic, showed a strength of 270 pounds, the upper limit on the scale of the instrument. Some idea of the force of such bites can be obtained from the fact that it takes a pressure between the teeth of about 73 pounds to crack filberts, from 110 to 140 pounds to crack Brazil nuts, and from 115 to 173 pounds to crack hazelnuts. Actually, only a few of the subjects could be persuaded to exert their full strength because their teeth soon began to hurt. Triska, working with dogs, found that when cracking bones they must exert pressure as high as 165 kg. (363 pounds) on each 10 sq. mm. of surface; most of the measurements ranged around 100 kg.

Swallowing. When the food has been sufficiently masticated and rolled up into a moist ball, it is forced back suddenly into the pharynx and then on down the esophagus. As the tongue pushes the bolus back, the nasopharynx is shut off by movements of the soft palate, and the epiglottis closes down like a lid over the top of the larynx so that nothing can enter the lungs (Küpferle). That this action of the epiglottis is not essential, however, is shown by the fact that persons can get along quite well after the organ has been

destroyed by disease or removed surgically. During swallowing, respiration is momentarily stopped.

The student who wishes to learn more about the details of this mechanism should read Chapters II, III, and IV in Cannon's book. He will find abstracts of the literature from the time of Hippocrates in an article by Eykman, serial roentgenograms of the pharyngeal phases of swallowing in articles by Scheier and by Küpferle, and roentgenologic studies, mainly of the lower esophagus, in articles by Hurst (1907), Kraus, Schreiber (1915), and Palugyay (1922 and 1923).

Influence of Gravity. It can easily be seen with the roentgenoscope that in man the mouthful is shot rapidly through the first part of the esophagus. It then drops, apparently under the influence of gravity, into the lower fourth of the tube, where it slows up for a moment before it slips through the cardia and into the stomach. The importance of gravity was shown by the experiments of Schreiber (1915) who found that when his subjects stood on their heads and tried to swallow, the barium mixture could no longer be pushed into the stomach. If enough was given, the esophagus filled and the upper edge of the column approached the cardia, but it did not pass it. Hurst (1907) watched the passage of cachets containing bismuth through the esophagus of subjects in the normal and in the inverted position, and found that with the force of gravity against them, these cachets went through the esophagus quite well until they reached the cardia, and there they remained for a long time. Palugyay (1922 and 1923) made similar studies and showed that if patients are put in the Trendelenburg position, the progress of material through the esophagus can be studied more satisfactorily because it is then seven times slower than normal.

Different Types of Activity. The earlier students of swallowing soon showed that there is more than one type of activity (Schreiber, 1901, Meltzer, 1907[a]). First there is a squirting of the food into, and down, the esophagus, brought about by the powerful muscles in the floor of the mouth; then there is a chain of reflexes instituted by the swallowing act; and, finally, there is a form of peristalsis which can arise at any point in the tube. The squirting activity is particularly important in

those animals that have to drink with the head down; the peristalsis originating in a swallowing movement is the commonest form, and the waves beginning in the lower parts of the tube serve to pick up and carry into the stomach bits of food which are left behind by the rushes that run from the pharynx to the stomach.

Certain animals show more of the squirting action and others show more of the peristaltic. In the goose it is all peristaltic (Cannon and Moser), and it takes twelve seconds for a bolus of cornmeal to travel 15 cm.; in the cat and dog

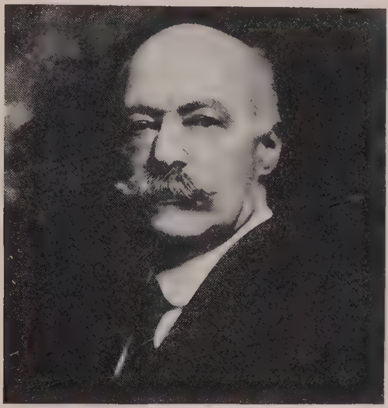

FIG. 21. Samuel J. Meltzer.

it is partly squirting and partly peristaltic for liquids, and purely peristaltic for solids (Cannon); and in the horse it is mainly squirting, even for solids.

That this squirting action is due to the mylohyoid muscles, and not to the constrictors of the fauces, was shown by Meltzer (1907 [b]) when he removed the entire musculature of the pharyngeal part of the esophagus and found that the dog could continue to drink liquids even with the head down. Cannon showed also that if the mylohyoids are cut or otherwise paralyzed in a mammal, it will have to raise the head in swallowing, just as a bird does. Schreiber (1915) came to the conclusion, however, that under normal conditions all the muscles in the floor of the mouth and in the pharynx help in

squirting material into the esophagus; naturally this action is not so marked in man as in those animals that have to drink with the head down.

The Nervous Control of Swallowing. Kahn (1903, 1906, and 1926) and Wassilieff have shown that there are a number of sensitive spots on the posterior wall of the pharynx from which the swallowing reflex can be started. In the dog and cat the chief spot is on the posterior wall of the pharynx, and is supplied by the glossopharyngeal nerve. Accessory spots on the upper surface of the soft palate are supplied by the glossopharyngeal and the second branch of the trigeminus, and others on the epiglottis are supplied by the superior laryngeal. These spots can be mapped by touching the mucous membrane here and there until the reflex appears; the chief spot is exceedingly sensitive and can set off one swallowing reflex after another. If these spots are anesthetized with cocain the subject may be unable to swallow for a while.

As is well known clinically, the mechanism of swallowing is often thrown out of order by injuries to nerves and to the nuclei in the floor of the fourth ventricle. Such disturbances are seen commonly with cerebral thrombosis, diphtheria, and botulism. They result in the regurgitation of food into the nose, and in its penetration into the larynx, with resultant spells of coughing and sometimes aspiration pneumonia. It is an interesting fact that the roentgenologist is sometimes the first to make the diagnosis of a bulbar lesion because he sees traces of a barium meal in the bronchi.

The Nerves of the Esophagus. The normal activity of the esophagus is highly dependent on the integrity of the vagi. When they are cut or damaged, that part of the wall of the tube that is supplied by striated muscle becomes paralyzed, and the chain of reflexes that normally carries food into the lower end of the esophagus is broken. So far as most investigators have been able to determine, the sympathetics have little effect on the movements of the tube (May, Inaoka, 1924, Jurica, 1926), but as will be seen from the work of Carlson and his associates, they do have some influence.

Stimulation of the vagus on either side causes strong tetanic contractions of the whole tube. According to Kahn

(1906[b]) and Caballero, the irritability of the esophagus, as shown by its responsiveness to the presence of a balloon, increases from the pharynx to the cardia. As Meltzer (1899) and many others have since pointed out, anyone who wishes to study the mechanism underlying the process of deglutition must avoid the use of anesthetics because they interfere so markedly with the proper working of the many reflexes which are involved.

Mosso (Cannon, 1911[a]) showed years ago that if the esophagus is cut across and a small wooden ball placed below the point of transection, and the animal then made to swallow, the wave coming from the mouth jumps the gap and carries the ball on into the stomach. This was confirmed by Meltzer (1899) who later was able to point out differences between the nervous mechanisms that control the two main types of esophageal peristalsis.

Cannon showed that in those animals in which the lower end of the esophagus is supplied by involuntary muscle, there is a certain amount of return of activity within a few days after the vagi have been cut, but in those animals, like the rabbit, in which the entire tube is lined by striated muscle, the paralysis that followed the operation seemed to be permanent. As Jurica points out, however, the striated muscle does not degenerate, and in the cat, after three months, there is some return of motility even in the upper portion of the esophagus.

Sensation in the Esophagus. The mucous membrane of the esophagus is not very sensitive to irritants, but painful sensations can sometimes be felt, and are usually referred upward into the neck, or downward to the epigastrium (Boring). According to Hurst, fairly strong solutions of hydrochloric acid are not felt in the lower end of the tube, but according to others, they may sometimes be felt, probably in highly sensitive individuals. The fact that food often regurgitates into the esophagus and that its acidity ordinarily is not perceived would indicate that the esophagus is normally rather insensitive. The pharyngeal end of the tube is probably sensitive to the acid, as anyone knows who has ever vomited or who has experienced what is commonly

called waterbrash. L. R. Müller (1920) has gathered a good deal of evidence to show that the feeling of thirst is due to strong spasmodic contractions of the esophagus.

Reverse Peristalsis. Reverse peristalsis in the esophagus of man has been observed only in the presence of disease. Carlson (1926) saw it once above a stricture. Frequently during roentgenoscopic examinations, especially in cases of cardiospasm, one sees the barium mixture shooting up even as far as the mouth, but I have always had the impression that this was not due to peristalsis but to sudden powerful contractions of the lower end of the tube.

Ripples of reverse peristalsis running up the esophagus are probably common, especially in persons who suffer from indigestion; if very shallow they may be perceived by the subject only as little gurgles which run out the eustachian tubes to the ears; when they are deep and strong they produce true belching and acid regurgitation.

Globus hystericus is due probably either to tonic spasms in the esophageal muscle or to the meeting of ascending and descending waves. On a few occasions I have happened to swallow about the time that a reverse ripple was starting up, and the meeting of the two waves produced a decidedly unpleasant sensation. The observations of Ivy and Vloedman suggest that during the intervals between digestion, tonus waves spread from the stomach up the esophagus.

The Pressure in the Esophagus. The normal esophagus generally contains some air, and it may be seen to dilate a little with each inspiration. According to Mikulicz, Schlippe, and Schreiber (1911[b]), the pressure in the esophagus is generally a little less than atmospheric, or about -3.5 mm. of mercury. It may be that this helps somewhat in allowing the food to be shot through from the mouth.

Air-swallowing. Many birds, such as the pouter pigeon, the man-of-war bird, and the grouse, have the faculty of distending the esophagus with air during the mating season. The confirmed belcher, that is, the man who can keep it up for an hour at a time, somewhat resembles these birds in that he has learned the trick of inflating and deflating the

esophagus; only rarely does he get any air in or out of the stomach (Chapter XXVI).

Dysphagia. This may be due to a number of conditions. With bulbar lesions food tends to enter the larynx, and the patient generally has trouble with choking and coughing. With hysterical dysphagia, as Vinson (1922) has pointed out, the subject is a nervous woman who finds it impossible to swallow solid food. Strange to say, such patients can be cured by one passage of a sound. The patient with cancer of the esophagus has trouble with swallowing, first solids, then gruels, and finally liquids. After the symptoms once appear there is no let-up until either an instrumental dilation or death brings relief. The patient with cardiospasm generally tells a long story of more or less intermittent difficulty with swallowing, and with the fluoroscope it can be seen, first, that the obstruction is at the cardia, and second, that the sides of the terminal funnel are smooth. Strictures, due generally to the swallowing of lye, are found in the middle region, and diverticula are found usually at the upper end where the left bronchus crosses the esophagus.

The Anatomy of the Esophagus. The esophagus is interesting in that the muscle, at least in the upper part of the tube, is striated. In rabbits this semivoluntary muscle extends a little way onto the stomach; in the goose it is absent, and in man and in cats and dogs it extends down for about two-thirds of the distance. This muscle seems to be a little different from other striated muscle in that it does not atrophy when the nerves are cut, and in this regard it resembles that of the external sphincter of the anus. Its physiologic peculiarities have been described by Goodall.

Surgeons who contemplate operating on the esophagus will be interested in the studies of Demel on the circulation of the tube. Other important details about its structure are to be found in the third volume of Ellenberger's work on the comparative anatomy of domestic animals (p. 138), and in articles by Thieding and L. R. Müller (1920).

CHAPTER XI

THE CARDIA

According to Zaaijer, who has made a particular study of the cardia, there is so little increase in the thickness of the muscle at that point that one can hardly speak of a true sphincter. The efficiency of the valve doubtless varies in different persons, since some regurgitate and vomit with ease, while other do these things only with the greatest difficulty. A review of the comparative anatomy of this region, well depicted in Huntington's remarkable book, leaves me with the impression that the weakness of the cardiac sphincter of man is probably an inheritance from the many lower forms of life in which there is little division between the cavities of the esophagus and the stomach, and in which the disgorging of food is physiologic. I refer particularly to the condition in many fishes, and in those birds that feed their young with regurgitated material. The one animal that should have a powerful cardiac sphincter is the insectivorous bat, because it does all its digesting during the day when it hangs upside down. Actually, H. Fischer has shown that these animals do have a powerful cardia which looks like the pylorus of other animals. They have had it for so many geologic ages that it appears now in the embryo.

Ordinarily, in man, the cardia does not seem able to resist the pressure of even a small column of liquid coming from above; and, similarly, I have seen barium water run back out of the stomach simply because the subject was placed in the Trendelenburg position. I have known, also, several persons who could not bend over without having food regurgitate into the pharynx. According to Cannon and Lieb, Veach, and others, the upper end of the stomach and the cardia relax as the subject swallows; this can easily be shown with the help of a recording balloon. I have not been able to show it with recorders fastened to the outside of the stomach, and records obtained in that way show only a wave of contraction running out a little way from the cardia.

Cardiospasm. Cannon (1906[a]), Carlson, Boyd, Pearcy, and others have found that the cutting of the vagi in the neck will produce a temporary spasm of the cardia and it may be that changes in the vagi are responsible for some of the cardiospasms seen in clinical practice. Against this view is the fact that the transient spasm seen after cutting the nerves is generally soon replaced by marked relaxation of the sphincter. Another possible cause for the disease as it is seen in patients is a reflex contraction such as Carlson, Boyd, and Pearcy obtained after strong stimulation of the sensory nerves of the abdominal viscera. Cardiospasm, however,

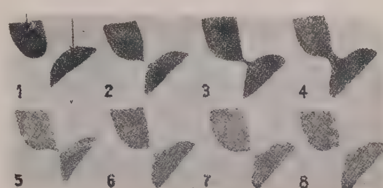

FIG. 22. Phases of the passage of food through the cardia as depicted in serial roentgenograms. (*From Palugyay.*)

often lasts for thirty years or more, and it is questionable whether a reflex closure could be maintained that long. It is hard to understand also why one dilatation of the sphincter should cure so many of these patients: in Vinson's experience about 75 per cent. This makes it look as if the contraction were in the tough submucous coat.

Mild degrees of spasm at the cardia are seen commonly in cases of gallbladder disease which may act either by stimulating afferent nerves or by raising in some way the tone of the whole digestive tract; more rarely they are due to ulceration of the upper portion of the stomach which stimulates the fibers in the neighborhood of the cardia. The student who wishes to go further into this subject will do well to consult the encyclopedic article of Thieding. There he will see that there are several types of cardiospasm with many different causes. Much work on the treatment of the disease has been done by Vinson (1926).

A Sphincter at the Orifice of the Diaphragm. Some writers, among whom may be mentioned Gubaroff, Kelling (1901),

Sinnhuber (1903), and Caballero, have felt that a large part of the sphincteric action at the cardia must be due to the contraction of diaphragmatic fibers surrounding the lower end of the esophagus. This now seems improbable because it can be seen with the roentgen ray that the sphincter is generally situated some 2 cm. below that point. Besides, as Schlippe has pointed out, the diaphragm contracts powerfully during the process of vomiting and yet the food leaves the stomach. The question of the control of the cardia during vomiting will be discussed in Chapter XXIII.

The Strength of the Sphincter. As Kelling (1901) has shown, it ordinarily does not take much pressure on the gastric side to force material back through the esophagus, but when an animal is deeply anesthetized, this ability of the cardia to relax is lost, and the stomach can then be inflated to bursting before the air will escape. This is probably an important factor in the production of acute dilatation of the stomach in man. I have seen such dilatation appear several times in animals with the abdomen open under salt solution; the air seemed to be getting in through the cardia but I could not push it out until a stomach tube had been passed.

Rhythmic Tendencies. The muscle at the cardia shows at times a marked tendency to contract rhythmically, and I have often seen the so-called Basslinger's pulse in the freshly excised stomachs of rabbits. This pulsation consists of a rhythmic pulling downward toward the center of the stomach of the lower end of the esophagus. A similar movement has sometimes been observed in man, during the process of swallowing.

Regurgitation. Cannon (1902) early noticed in cats a rhythmic regurgitation from the stomach into the esophagus which could be seen with the help of the roentgen ray. The barium mixture runs up to the level of the heart and sometimes even into the neck, and then back again. It takes place without any sign of reverse peristalsis and seems to be due to quick contractions of the lower esophagus. He found that this process could be stopped by acidulating the contents of the stomach, and concluded from this that the cardia must be under an acid control similar to that which he

thought existed at the pylorus. So far as I know, the only one who has attempted to corroborate these findings is Carlson, and he failed to get results like those of Cannon. Burnham studied the similar form of regurgitation that can be seen sometimes in man, and concluded that it occurs most commonly in cases of gallbladder disease.

Reflex Control of the Cardia. Carlson, Boyd, and Pearcy (1922) recently made a careful study of the nervous control of the cardia, and they have reviewed the literature on the subject. In unanesthetized dogs they have found that the tone of the sphincter can be inhibited temporarily by stimulation of the mucous membrane of the stomach, and particularly by stimulation of sensory nerves in the mouth and pharynx. The tone increases during the progress of digestion, but not *pari passu* with the increase in the acidity of the contents. It increases also when the walls of the stomach are suddenly distended.

In lightly anesthetized or decerebrate dogs, reflex changes in the tone of the cardia can be produced by stimulation of sensory nerves anywhere in the body. When the vagi are intact, stimulation of sensory nerves in the mouth and pharynx and in the mucous membrane of the esophagus and stomach usually induces inhibition followed by contraction. Stimulation of afferent nerves in the abdominal viscera usually causes contraction, even when the vagi are cut. As so commonly happens with smooth muscle, when the initial tone is low, the response obtained tends to be a motor one, and when it is high, the response is generally inhibitory.

Atropin abolishes the action of both the vagi and the splanchnics on the cardia and lower esophagus. Epinephrin has both motor and inhibitory actions on the cardia and esophagus of the dog and cat. In the rabbit its action is purely inhibitory. Again, the nature of the response depends largely on the initial tone of the muscle. It would be well if many clinicians would read Carlson's conclusion that the prevailing view in regard to an antagonistic action of the vagus and splanchnics is not tenable in the case of the cardia and the stomach.

CHAPTER XII

GRADED DIFFERENCES IN THE STOMACH WALL

When it was seen that the rate of rhythmic contraction in the small intestine varies inversely as the distance from the pylorus, the next question was: How about the other parts of the digestive tract? Could the *primitive digestive tube* have been constructed originally so that the rate would be highest at the pharynx and lowest at the anus? Although this question cannot be answered conclusively as yet, there is considerable evidence in favor of the view that the whole tract once showed such a gradation (Alvarez, 1916[a]). Thus, the rates of contraction in different parts of the colon of the rabbit and cat fit quite well into a prolongation of the curve plotted from the rates in different parts of the small bowel. These rates vary in the rabbit from 6 to 10 per minute near the cecum to from 3 to 5 per minute near the anus.

It is impossible to say much about the esophagus in mammals because in them that tube is made up almost entirely of striated muscle, and the smooth fibers appear only in the lower third or fourth. Longitudinal segments from the lower end of the esophagus of laboratory animals show a high rhythmicity when placed in oxygenated Locke's solution. The fastest rate observed in the cat was 14 per minute and in the rabbit 19 per minute. As we should expect if my hypothesis is correct, these rates are higher than those for the excised duodenal segments in these animals. In the frog's esophagus, where the muscle is all of the smooth variety, we can see that the rate of rhythmic contraction varies inversely as the distance from the pharynx. I have shown these differences also in the esophagus of a snake. In the frog the esophageal rate was generally faster than that of any other part of the digestive tract.

Even if further work on animals should show definitely a gradation of rhythmic activity from pharynx to anus, we should still have to explain the low rate of the gastric waves in mammals: from 3 to 4 per minute in the rabbit, dog and

man, and from 4 to 6 per minute in the cat. A possible way out of this difficulty is suggested by the literature on another muscular tube—the heart. Gaskell (1900) looked on that organ as an elaboration of a simple tube which has become twisted on itself and has bulged in places. There the muscle has become specialized so that it can contract and empty its cavities more quickly, and there the "development of this nearer approach to striated muscle is made at the expense of the original rhythmical power." This may perhaps account for the fact that there are only 3 large waves per minute in the stomach, but little stress can be put upon this argument since Dr. Zimmermann and I have found in laboratory animals, that small waves with rates running between 15 and 30 per minute are commonly seen in the fundus.

THE PRIMITIVE DIGESTIVE TUBE AND ITS MODIFICATIONS

A glance at Figure 23 will show how the stomach also has been evolved from a simple tube: first by an enlargement; second, by a bending of the pylorus toward the cardia; and third, by the addition of one or more cecal pouches. The stomach of the eel consists almost entirely of such a pouch which has grown from the convex side of a bend in the original tube. It is obvious in such a stomach that the primitive tube is to be found along the lesser curvature. Even the complicated stomachs of ruminants can be resolved into a series of ceca arranged along the original tube (Oppel, Huntington). The fundus of the human stomach represents such a cecum which very early in life grows out from the greater curvature (Keith and Jones, Lewis, 1912, p. 500). Lewis shows that in a 10 mm. human embryo, the stomach is made up of three parts: the expanded, conical lower end of the esophagus; the long tubular antrum, a little wider than the adjacent duodenum; and a small fundus. The end of the esophagus meets the pyloric antrum at the incisura angularis. Later the fundus grows at the expense of the other two parts so that in the adult the end of the esophagus is represented only by the cardiac antrum and that prolongation along the lesser curvature which forms the gastric canal. Thus in the

adult, the pyloric antrum makes up a much smaller part of the stomach than it did originally (Fig. 23).

The primitive tube must accordingly be looked for along the lesser curvature. It is suggestive that this part of the

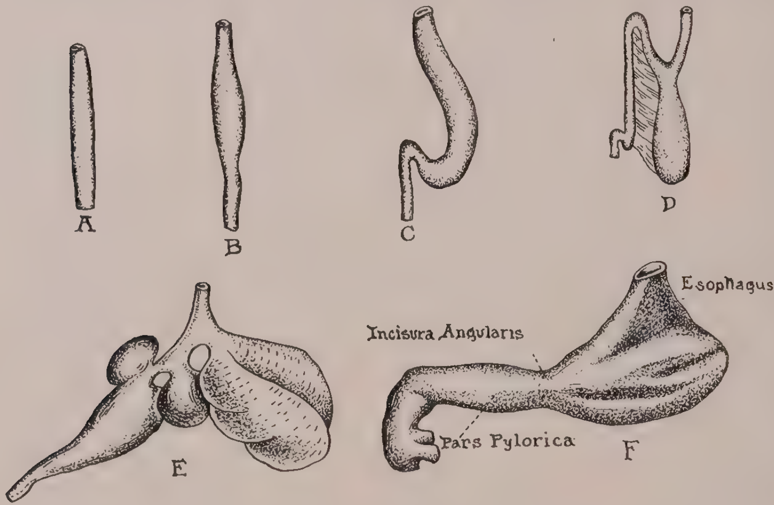

FIG. 23. Shows the development of the stomach. (*a*) Stomach of the pickerel (Nuhn); (*b*) stomach of Proteus anguineus (Nuhn); (*c*) stomach of Scincus ocellatus (Nuhn); (*d*) stomach of the eel (Huntington); (*e*) scheme of the ruminant compound stomach (Nuhn); (*f*) stomach of a 10 mm. human embryo (Lewis).

stomach is lined by an epithelium differentiated least of all from that of the intestine; that is, the glands are mainly of the pyloric type (Bensley, Lansdown and Williamson). A similar arrangement is found in most of the domestic animals (Haane). It is interesting also that many animals, including man, have a loop of muscle fibers along the lesser curvature which on contracting make a gutter, or in the ruminants and kangaroos an actual tube, which conducts fluids from the cardia to the pylorus. In this way the primitive tube is largely restored, and food is prevented from entering the cecal parts of the stomach. This tube is called the canalis gastricus (Jefferson).

If this idea of a pouch evolved from a primitive tube is correct, we should expect to find the most rhythmic tissue on the lesser curvature near the cardia. Actually, we do find it there (Alvarez, 1916[a]).

FIG. 24. Tracings of the shadow cast on the fluorescent screen by the stomach of a cat, showing changes in the shape of the organ at intervals of an hour during the digestion of a meal. Note the tonic shortening of the fundus, slowing pushing the food into the antral mill. (*From Cannon.*)

DIFFERENCES IN RHYTHMICITY

Differences in rhythmicity were shown by cutting off little strips of muscle from different parts of the stomach and getting them to contract in warm aerated Locke's solution. The segment from the lesser curvature next the cardia always showed the greatest tendency to rhythmic contraction. Strips from the greater curvature, and particularly from the pyloric antrum, were slow in starting; and many would not contract at all. The rate varied ordinarily from about 11 at the cardia to about 2 at the pylorus. In 1916, when I was studying the rhythmicity of these strips, I was puzzled by the fact that in the rabbit, the one taken from the region of the greater curvature opposite the incisura

showed a tendency to beat almost as fast as that from the lesser curvature near the cardia. This observation did not fit well with my idea of a gradient of rhythmicity running from the cardia to the pylorus, but recently, I have found that it fits well with evidence which will be discussed in the next chapter, all pointing to the presence of a region of high automaticity at the upper edge of the pars pylorica.

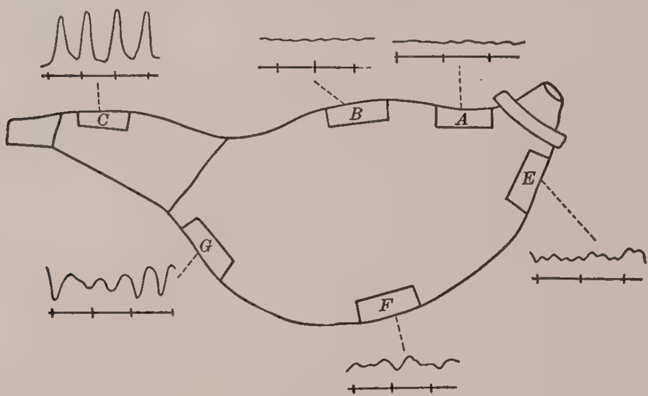

FIG. 25. A diagram of the cat's stomach to show the location of the principal strips studied and the types of tracing peculiar to the different regions. The time tracing represents thirty-second intervals.

It seems probable, therefore, that there are two gradients of rhythmicity in the stomach, one in the fundus and the other in the pyloric region.

Figure 26 shows that in the strips removed from the stomach of the dog, there is some sign of a gradient in the rate of rhythmic contraction running from the cardia to the pylorus, and it shows the marked differences in the shapes and amplitudes of the contractions in the different regions. On the lesser curvature the amplitude is small, while in the pars pylorica it is large. The figure shows also that these differences are just as characteristic in tracings from bits of muscle removed from the stomach of man. They have been observed also by Tezner and Turold who used human material. These workers were struck as I was by the sudden sharp rises from a constant base line in the records from the

pars pylorica, and the more irregular rounded contractions of the strips from the fundus. Even with the help of pilocarpin, Brown and M'Swiney could not get their strips of pyloric muscle to contract rhythmically. They found as I did, that the strips from the cardiac region had the greatest tendency to contract rhythmically, but they could not establish any gradient of rate down the stomach.

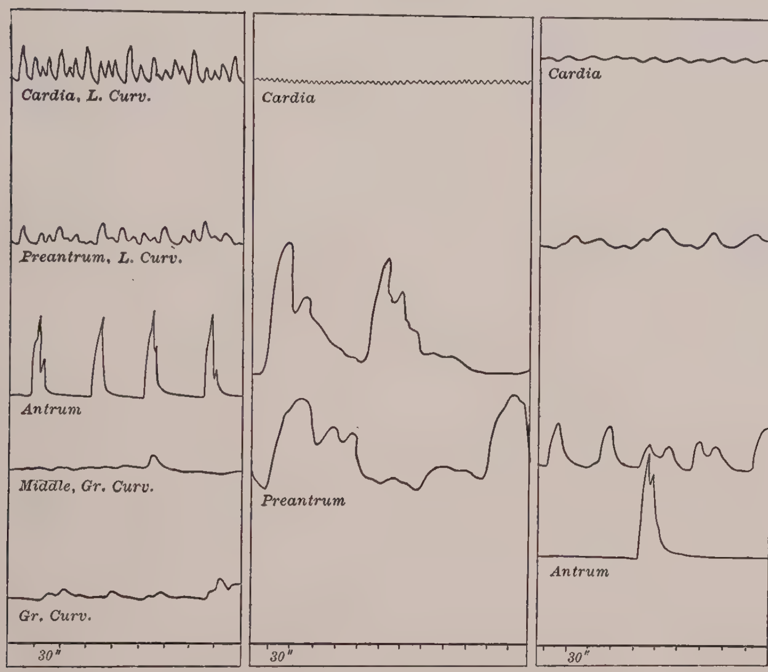

FIG. 26. Records from five strips from different parts of the dog's stomach; of three strips from the lesser curvature of the human stomach and from four strips from the greater curvature of the human stomach.

DIFFERENCES IN TONE

Differences in tone were observed while studying the strips of excised muscle. When the pieces were removed on the lesser curvature, not only did they contract markedly, but the edges of the cut retracted so that the piece was several sizes smaller than the hole. On the greater curvature, the

piece sometimes stretched a little and became even larger than the hole. The differences in the amplitude of contraction in the different segments may be ascribed partly to these differences in tone and partly to differences in the structure and arrangement of the muscle fibers.

DIFFERENCES IN IRRITABILITY AND LATENT PERIOD

A search of the literature showed that several men have observed local differences in the irritability of the gastric wall. Meltzer (1895) noted that the fundus was rather unresponsive and that the whole stomach was less sensitive than the bowel. Lüderitz (1891) noted that the contraction often appeared cardially to the stimulated place. He thought that the lesser curvature was more sensitive than any other place. He noted the peculiar type of reaction in the pyloric antrum, and the insensitiveness of the fundus. Ducceschi studied the irritability of the interior of the stomach and thought the reactions to mechanical stimuli were quicker and more energetic near the pylorus than anywhere else. The cardia, however, was most responsive to faradic stimulation, and its latent period was shortest. Weak acids also had a more pronounced stimulating effect on the cardia than on the fundus. In the pyloric antrum the effect was generally reversed, the active movements being inhibited. The presence of a balloon in the antrum almost always gave rise to active peristalsis; but this was not the case in the fundus. Waterston commented on the local differences in the response of the human stomach to the formalin in embalming fluid. He thought the pyloric sphincter and the upper end of the pyloric antrum must have the most irritable muscle. Carlson (1913) has noted that the hunger contractions are mainly in the fundus while the digestive contractions are mainly in the pyloric part. "Either these two regions of the stomach react differently to local stimulation of the gastric mucosa or else the nervous mechanisms concerned . . . are different." May found the inhibitory effect of vagus stimulation more pronounced on the cardia than on the pyloric end of the stomach.

Barbera's work is very important. He found that when the stomach of a frog is stimulated at any point by weak faradic shocks, the contraction appears first at the cardia. He found that this is due to a shorter latent period at the cardia, *i.e.*, 8.4 seconds, as compared with 10.2 seconds in the middle region, and 13.5 seconds near the pylorus. I confirmed this work of Barbera (Alvarez, 1916[b]), and showed also that the cardia is the most irritable part of the frog's stomach. Frequently stimulation of the pyloric region brought

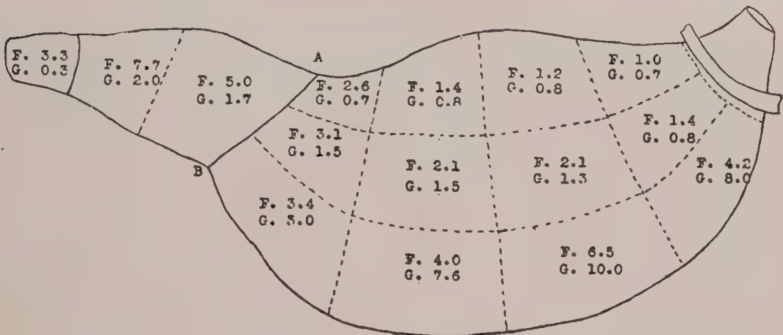

FIG. 27. Anterior surface of the stomach of the cat, showing the average latent periods after faradic and galvanic stimulation in different regions. The figures indicate seconds. *AB* is the dividing line between the pars pylorica and the body of the stomach. The other unbroken line represents the pylorus.

about contractions near the cardia and in the duodenum before any effect was observed under the electrodes.

Similar work was done on the stomachs, excised and intact, of rabbits, cats and dogs. The more satisfactory work was done on the excised stomachs because the irritability of the stomach in the intact animal, anesthetized, and with the abdomen open, is considerably lower than that of the organ when removed from the body and kept warm in a moist chamber.

In the rabbit, the reaction to electrical stimulation near the cardia is almost immediate. This is due largely to the fact that strands of striated muscle extend from the esophagus onto the stomach and 2 cm. beyond the cardiac

thickening. Figure 27 shows that the latent period lengthens as one passes from the cardia to the pylorus and from the lesser to the greater curvature.

The pyloric ring was more irritable, and showed a shorter latent period than did the rest of the antrum. This point should be emphasized, as it may have important clinical bearings. The duodenum, a few millimeters away from the antrum, responded much more promptly to the galvanic current. For some unknown reason, the difference was not so marked with the faradic current. There is a definite gradation in the ratio between the latent periods with the two types of current in different parts of the stomach; but the exact explanation for it must await further study.

Some work was done on *human stomachs* excised shortly after death, and *in situ* during abdominal operations, but the results were not very satisfactory. Enough was done to show the differences between the effects of faradic and galvanic stimulation in the antrum, and the differences in irritability between the stomach and duodenum.

Much of the sluggishness of the intact stomach seems to be due to nervous inhibition. If the irritability of the muscle were dependent upon its nervous connections, we should expect the reactions to become progressively slower after removal of the stomach from the animal, and particularly after the trauma of cutting the strips; yet the opposite is true. The latent period was often shorter, and the rhythmicity in all but the cardiac strip was generally much better on the second or third day than on the first. Good records were secured from bits of muscle removed from the stomach of an executed criminal and kept in Locke's solution at 10°C. for four days.

DIFFERENCES IN EXCISED SEGMENTS

There was a marked difference in the appearance of the contraction curves obtained by stimulating bits of muscle cut from the pyloric antrum and the cardiac region of the frog. The cardiac strips showed by far the greater rhythmicity (Alvarez, 1917[a]). They suffered more from the trauma of excision and they recovered slowly as compared with the

antral strips. They suffered more damage also from strong faradic currents. They did not stand being kept in the ice box so well as did the strips from the antrum. Strips from the middle of the frog's stomach reacted more like those from the cardia than like those from the antrum. The muscle in the antrum of the frog's stomach is firmer to the touch and there is a marked difference between it and that in the rest of the stomach. Many of these findings have been confirmed by Gellhorn and Budde.

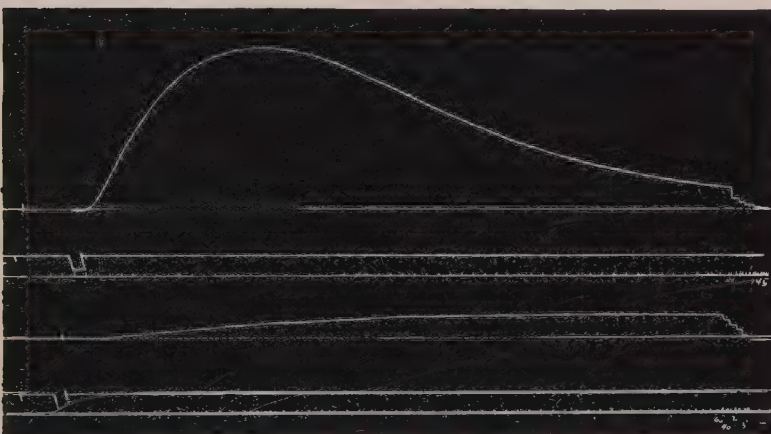

FIG. 28. Contraction curves from strips from the frog's antrum (upper) and the cardia (lower). The same strength of faradic current was used. Time markings represent seconds. Magnification of lever 4.5:21.

Similar differences were found in the reactions to artificial stimulation of strips of muscle excised from different regions of the stomachs of cats, dogs, and rabbits (Alvarez, 1917[b]). Speaking roughly, the latent period varied as the distance from the cardia. The shape of the contraction curve was different and characteristic for the various regions of the stomach (Fig. 28). The muscle from the fundus showed a great tendency to remain tonically contracted after stimulation, while the antral muscle relaxed promptly. The muscle in the pyloric antrum seems to be particularly fitted to carry on the active work of the stomach, while the fundus

serves to maintain a steady tonic pressure on the contents The muscle from the antrum has a color different from that in the rest of the stomach. It is redder and tough like that of a gizzard. The muscle from the pacemaking region is soft to the touch like coagulated fibrin. Todd (p. 95) says that the muscular fibers in the pyloric region are bulkier and more separate from each other than is the case in the cardiac portion of the stomach.

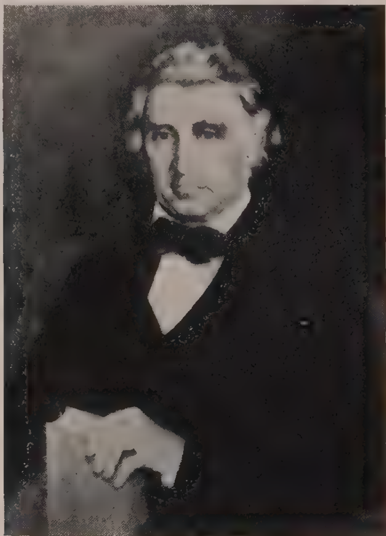

FIG. 29. William Beaumont.

When the strips were left for forty-eight hours in the ice box those from the antrum showed themselves peculiar in that their latent periods were shortened while those of the other strips were more or less lengthened. In diseased animals all but one or two strips generally showed a lessened irritability and a lengthened latent period. In some of these sick animals the latent period of the antral strip was definitely shortened. This lengthening of the latent period at the cardia with a shortening at the pylorus often produces a reversal of the normal gradient.

DIFFERENCE IN CATALASE CONTENT

I have already commented on the gradation in the catalase content of the muscle from the duodenum to the ileum. A similar gradation was found in the stomach (Alvarez and Starkweather, 1918[c]). This gradient was more marked along the lesser curvature than on the greater. In the rabbit the amount of catalase was larger along the lesser curvature than along the greater. For some unknown reason this ratio

FIG. 30. Walter B. Cannon.

was reversed in the cat and dog. Further work needs to be done on the metabolism of the muscle in the stomach wall.

DISCUSSION

It has been well established by many workers that the stomach performs its functions after section of the extrinsic nerves (Cannon, 1906[a], p. 429; Rubaschoff, Krehl), and even after its removal from the body (Hofmeister and Schütz, Cannon, Alvárez). We see now that local peculiarities in the muscle, with graded differences in rhythmicity, irritability, tone and latent period probably have most to do with directing the peristaltic wave as it travels over the stomach. As in the heart, so here, the waves probably have their

origin in the most highly rhythmic and sensitive area. We may say perhaps that the region on the lesser curvature next to the cardia is the pacemaker for the stomach. It must be remembered, however, that the activities of the heart and stomach are very different. In one, the impulse travels so rapidly that the organ appears to contract as a unit; in the other a series of waves travel slowly over the sac, gently kneading its contents.

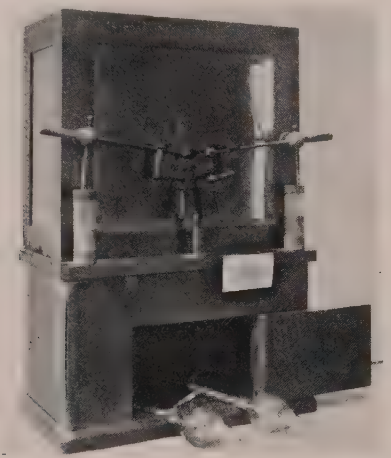

Fig. 31. Frictional machine and tubes used by W. B. Cannon in his first work; now in the Warren Historical Museum, Harvard Medical School.

A glance at one of Groedel's (1912) illustrations (Fig. 32) made up of the superimposed outlines of a dozen serial roentgenograms of the same human stomach, will show how little the lesser curvature, as far as the incisura angularis, is affected by the peristaltic waves. The amplitude is very small, just as it is in excised segments of muscle from this region. Appearing at a variable distance from the fundus, the gastric waves seem to travel almost entirely along the greater curvature, getting deeper as they approach the antrum. At that point their character changes: they involve the whole circumference of the stomach and become so deep that they almost meet in the center. It seems to me that these local differences in the shape and depth of the peristaltic wave

correspond perfectly to the regional peculiarities in tone and amplitude of contraction of the muscle fibers through which it must pass. The reader may grasp the idea more easily if he will think of an impulse traveling down a series of wires, the tension of which varies inversely as the distance from the top. At the upper end the waves will have a low amplitude and a high frequency, while at the lower they will have a large amplitude and a low frequency. It is interesting

FIG. 32. Shows the superimposed outlines of a number of gastric roentgenograms taken serially. Note the small amplitude of contraction in the upper part of the stomach and the change in the character of the waves when they reach the pyloric antrum. (*From Groedel.*)

in this connection that Jenkins and Carlson say, after studying the muscles of a number of molluscs, that "the rates of nervous impulse and forms of the myograms of the three well express the differences in the degree of activity manifested by the three." The squid is the most active simply because it has the most efficient muscles.

In the heart, when the sinus node is damaged, the tissue with the next highest rate assumes the pace. Dittler noticed a similar shifting in the crop of the sea slug Aplysia; and we know that waves will run aborally over the pyloric portion of the dog's stomach even after it has been separated from

the cardiac end (Kirschner and Mangold). There is little interference with peristalsis in the human stomach after so-called sleeve resections of the middle portion (Faulhaber and von Redwitz, 1914); and Cannon has shown that waves will keep traveling over the organ quite normally after the healing of several encircling cuts which have been made through the muscle extending down to the mucosa (Cannon, 1911[d], p. 258).

Rather against the view that the waves originate near the cardia is the common observation that they seem to appear now here, now there, on the greater curvature. Cannon (1911[d], p. 257) felt that the pulsatile source of the gastric wave has no fixed seat. He thought that the waves probably appear at levels where a certain balance is struck between the tone of the muscle and the internal tension. In some of my records, however, I have been able to show that those waves that seem to arise in the lower third of the stomach are really parts of ripples that have come down, unperceived by the eye, from the region of the cardia.

One question that remains is: Why should the rates of contraction of the strips excised from the stomach be so much faster than the rate of the peristaltic waves in that organ? I am inclined to think that the contractions of the excised strips correspond to the wavelets seen in the intact stomach, while the peristaltic waves arise in a tonus rhythm similar to that which is found in the bowel (Alvarez, 1925), and which generally has the small swaying movements superimposed upon it.

CHAPTER XIII

THE MOVEMENTS OF THE STOMACH

The Way in Which Waves Travel over the Stomach. It is a remarkable fact that with all our advances in knowledge, we are still uncertain as to the exact way in which the waves of the stomach travel to the pylorus. Most of the older writers, influenced partly by the observations of Beaumont on Alexis St. Martin, and partly by the experiments of Hofmeister and Schütz on excised stomachs, taught that the contractions traveled peristaltically until they reached the upper margin of the pars pylorica; there a transverse band was supposed to close down so forcibly as almost to divide the stomach into two pouches, and the lower one then contracted systolically. Later, as the roentgen ray and barium meal came more and more into use, this idea of a systolic contraction of the antrum was largely given up in favor of the view that the waves travel peristaltically all the way to the pylorus.

Cannon came to the conclusion that a complete division of the stomach by the so-called transverse band must be the result of some unnatural stimulation. "Many times I have carefully watched with the *x*-rays gastric peristalsis in human beings, monkeys, dogs, cats, white rats, and guinea pigs, and although the waves moving into the pyloric half of the vestibule have at times almost obliterated the lumen, I have never seen such deep constrictions at the beginning of the pyloric portion. The systole of the vestibule in the rabbit I have noted in one instance, but I have also watched in the rabbit's stomach continuous peristalsis running from the middle of the organ to the pylorus as in the other animals, without any obliteration of the gastric lumen." (1911[b], p. 53.) These views were confirmed by the roentgen-ray studies of Roux and Balthazard, of Kästle, Rieder, and Rosenthal and others, so that by 1911 Cannon felt that the earlier idea of a transverse band and an antral systole could be given up.

Actually, as so often happens when competent observers disagree, both groups were partly correct. When in 1912 I began roentgenoscoping the stomachs of men and women I soon saw that the gastric waves did not always approach the pylorus in the same way; some traveled peristaltically right to the sphincter; others either faded out a short distance above it, or else seemed to be blocked by a contraction

FIG. 33. Shows the superimposed outlines of a series of roentgenograms taken at short intervals. The subject was suffering from tabes dorsalis. The waves traveled peristaltically to the pylorus. (*From Groedel.*)

which appeared at the pylorus a little ahead of time; and others gave rise to a systolic contraction of a considerable portion of the antrum. Not infrequently, contractions appearing in the mid-region of the stomach did not progress, or else traveled a little way and then faded out. Lasting, cramplike contractions of the pars pylorica were seen occasionally in cases of subacute gallbladder disease; and reverse waves were seen in a few patients with ulcers near the pylorus.

As has already been noted, the serial roentgenograms of Kästle, Rieder and Rosenthal showed peristaltic waves traveling right to the pylorus. Groedel, however, using the same technic, obtained pictures like those in Figure 32 which show clearly that the peristaltic wave, deepening as it progresses, travels caudad until it reaches a point a few centimeters above the pylorus, and there gives rise to a systolic contraction of the pars pylorica. A few pages further on in his interesting atlas, he gives an example of the purely peristaltic type of wave, but strange to say, the plates reproduced are those of a patient with the gastric crises of tabes. Still another type of peristalsis pictured by Groedel is one in which waves begin near the incisura and travel very shallowly to the pylorus.

In America, the pioneer in serial roentgenography is Cole. In a recent letter to me he expresses his conviction that normal peristalsis in man consists of waves which travel peristaltically over "all parts of the stomach except the pyloric canal"; and his published plates and animated motion pictures show them going down to a point about 2 cm. from the pylorus. He emphasizes the existence of gastric cycles, during which "the stomach goes through a series of shapes and comes back to the original one," and he was the first to point out that, at intervals, all the peristaltic indentations become deeper or shallower, coincident apparently with systolic and diastolic changes in the musculature of the whole organ.

Carman, from his enormous experience with the roentgenoscopic technic, concluded that Kästle, Rieder and Rosenthal were probably right, and that the waves in man generally go to the pylorus. He expressed doubt as to the existence of systoles.

Evidence Obtained with the Electrogastrograph. The first electrogastrograms which Miss Mahoney and I obtained in 1921 (Alvarez, 1922[a, b]) showed that the problems of gastric peristalsis were even more complex than I had suspected from the observations with the roentgen ray. Thus, we were able to show that although some of the waves that seemed to begin a little above the incisura had really come as ripples

all the way from the region of the cardia, others seemed to be starting here, there, and everywhere on the surface of the stomach, and traveling in different ways to the region of the pylorus. Not infrequently, we found signs also of a marked dissociation between the activities of the fundus and the pars pylorica; sometimes there was a blockage of one or more waves but, occasionally, there seemed to be a complete independence of the rhythmic activities in the two regions,

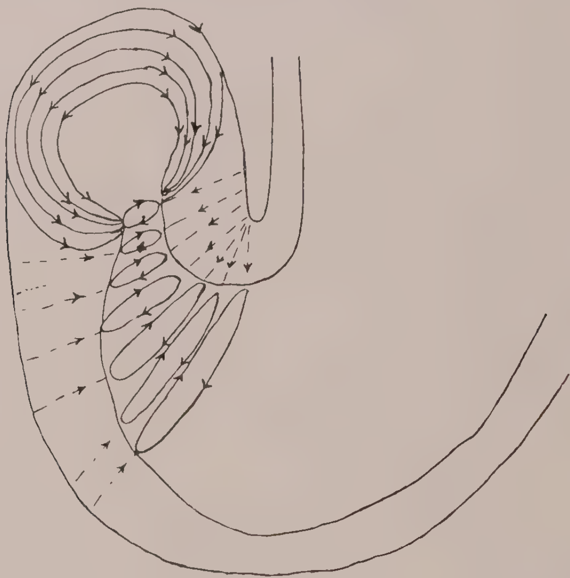

FIG. 34. Diagrammatic analysis of serial roentgenograms of the pars pylorica. (*From Groedel.*)

with the fundus contracting about three times to the antrum's once. (See Figures 36 and 37.)

That this sort of thing could occur in man was suggested by the finding of two types of deflection in the electrogastrograms from a human subject; one with a rate of three times a minute, corresponding exactly with the waves of peristalsis visible through a thin abdominal wall, and the other with a rate of eleven times a minute, corresponding probably with small waves in the fundus.

Graphic Records of Gastric Peristalsis. Later, as Figures 38 and 39 will show, we were able to demonstrate with mechanical recorders all the peculiar types of gastric activity which had been detected with the galvanometer, and we no longer had doubts about the existence, at least in the anesthetized animal with the abdomen open under salt solution, of all sorts of combinations of peristaltic waves, systoles, tonus waves, wavelets, and reverse waves. No doubt

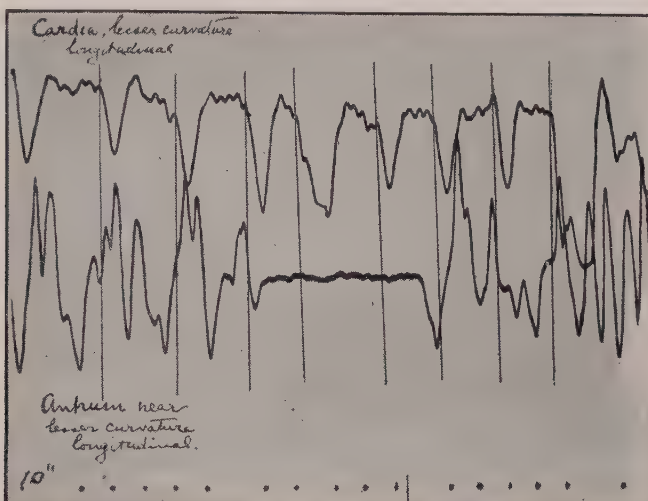

FIG. 35. Electrograms from the cardia and pars pylorica of a cat. The small deflections on both records are probably respiratory in origin. In this and in all other electrograms an upward movement indicated a negativity of the orad electrode. Note blockage of two waves.

remained either about the frequent dissociation of activity between the two halves of the stomach, or about the existence of independent wavelets and larger tonus changes in the body of the stomach.

Unfortunately the tracings are still hard to interpret, not only on account of the great variety in the types of contraction depicted, but on account of the difficulties in recording simultaneously the activities of enough segments of the organ studied. If the cycle of contraction always repeated itself exactly, as it does in the normal heart, we

could analyze the movements in one small area after another and then fit our tracings together; but unfortunately, in the

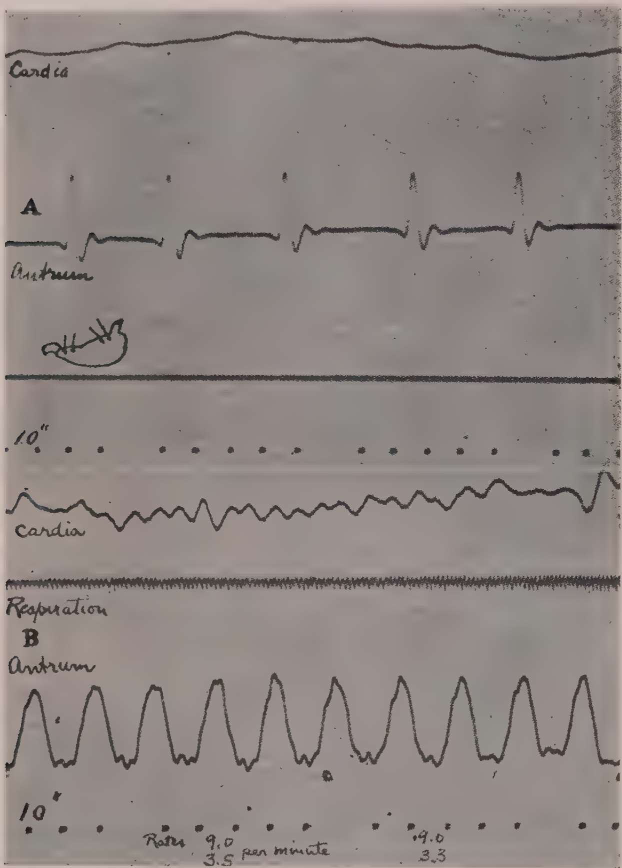

FIG. 36. A, simultaneous electrograms from the excised stomach of a cat. Note that waves in the antrum probably come as otherwise imperceptible ripples from the cardia. B, simultaneous electrograms from the stomach of a cat under urethane anesthesia and with the abdomen opened under Locke's solution. Note dissociation between the activities of the two parts of the stomach.

stomach, the combination of descending peristalsis and local contractions is a constantly changing one, and in order to

learn what we want to know, I think we shall have to have simultaneous records of the movements of dozens of points.

Motion Picture Records. The only way in which we are likely ever to get such complete records is by taking motion pictures. Small markers can be fastened on many points over the surface of the stomach and, later, the varying distances between these points in successive pictures can be plotted as ordinates, with intervals of time as abscissas, and the records so obtained will correspond closely with those made with the help of heart levers. Dr. Zimmermann and I have for some time been attacking the problem in this way and we have already obtained tracings which we think will go far toward clearing up the doubts and perplexities of the past.

A Solution of the Problem. When we analyze these new records of gastric peristalsis, we no longer wonder at the disagreement between the various workers because it is hard to imagine a phenomenon more cunningly designed to deceive the observer. The curves in Figure 41, which represent the movements of the lower end of a dog's stomach, show that while the wave in the longitudinal muscle runs peristaltically all the way to the pyloric line, the wave in the circular muscle changes into a systole, or perhaps we should say simply that the ring near the sphincter contracts ahead of time because the muscle there has a shorter latent period. As if this were not confusing enough, the muscle next to the pylorus, which begins to contract at the same time as the segment just above it, often shortens so much more slowly that if we look only at the peaks in the record we will think that we are dealing with a simple peristaltic wave.

We now have photographic records of scores of gastric waves in dogs, and so far they all show this systolic type of contraction in the circular fibers of the last centimeter or two of the stomach. The point at which the waves change into systoles varies, however, in different animals, and from time to time in the same animal. In one dog we saw the typical contraction of the transverse band described by the old physiologists. Sometimes this contraction relaxed after a few seconds and at other times it was followed by a systolic contraction of the pyloric half of the stomach. The pictures

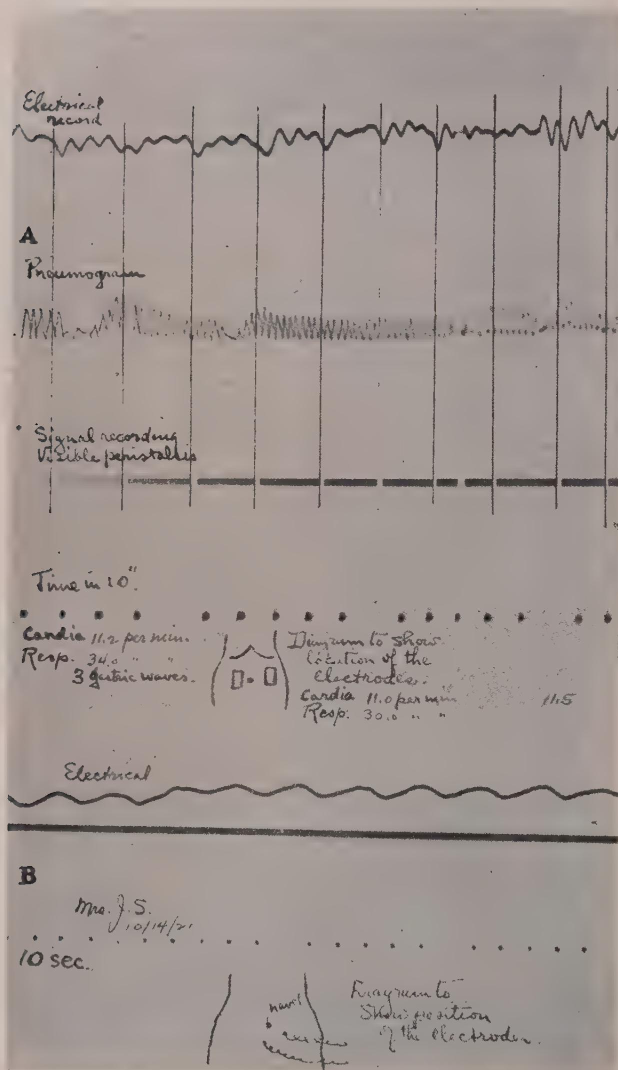

FIG. 37. Human electrogastrogram. A, the small frequent, fundus type of deflection superimposed upon larger deflections which correspond in time with the visible gastric waves. B, the antral type of deflection. The small diagrams show where the electrodes were placed on the abdomen.

show also the dissociations between the activities of the fundus and pars pylorica which I discovered in the electrogastrograms, and they show small waves, probably of local origin, superimposed on the larger peristaltic ones.

For years I have puzzled over the fact that the peristaltic waves sometimes seem to hesitate or lose time as they cross

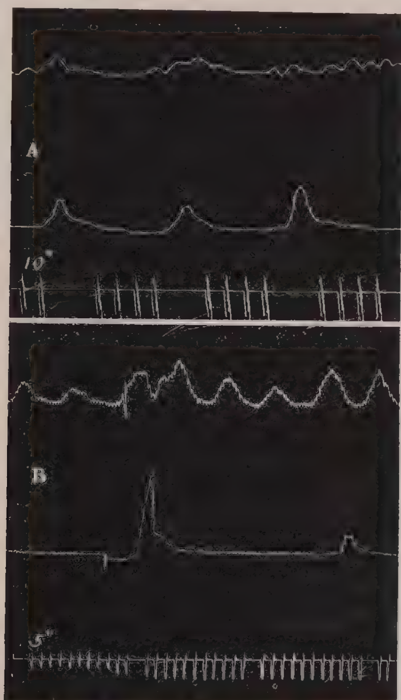

Fig. 38. A record obtained by fastening levers to the peritoneal surface of the excised stomach of a dog kept in warm Locke's solution. Note dissociation between the activities of fundus and pars pylorica, and the block with an occasional escape. The small waves in the preantral record are respiratory in origin.

from the body of the stomach to the pars pylorica, and the new records suggest, as I suspected, that this is due to a difference in the rate of conduction of the wave in the two parts of the stomach. Most interesting also is the fact,

hardly suspected before, that the small contractions on the fundus near the cardia resemble the rhythmic segmenting movements of the upper bowel. I have records also of ripples running orad over the body of the stomach with deep waves running caudad over the pars pylorica.

Recent Literature on the Gastric Movements. As so often happens in the progress of scientific discovery, a subject which has lain for some time dormant suddenly awakens the interest of a number of workers throughout the world; hence it is, probably, that in the last few years a group of papers have appeared in which the fact has been recognized that the mechanism of gastric motility is not simple, and that even in health, peristalsis can follow first one pattern and then another. The correctness of most of these observations is particularly remarkable in view of the fact that none of the workers obtained graphic records of the phenomena which they studied.

In 1920, Wheelon and Thomas observed in dogs with the abdomen open, the fading out at the incisura of some of the peristaltic waves, the apparent pausing of waves there, the dissociation between the activities of the two parts of the stomach, and the systolic type of contraction in the pars pylorica. They concluded, however, that the continuous type of peristaltic wave was the normal one for the moderately filled dog's stomach, and they never saw a systole of the whole pars pylorica. They mention a wave of relaxation following the wave of contraction, something that I have long observed but never could analyze satisfactorily until I recorded it with motion pictures.

M'Crea, M'Swiney, Morison and Stopford used cats, rabbits and dogs, and either watched the movements with the abdomen open, or else gave barium meals and used the roentgen ray. They describe waves which began near the cardia and spread downward, producing a constriction ring at the upper end of the pars pylorica, then a bulging of the pyloric portion, and finally a concentric contraction of that region. This contraction relaxed as a new wave arrived at the incisura. In some instances small waves could be seen traveling over a contracted antrum, and at other times,

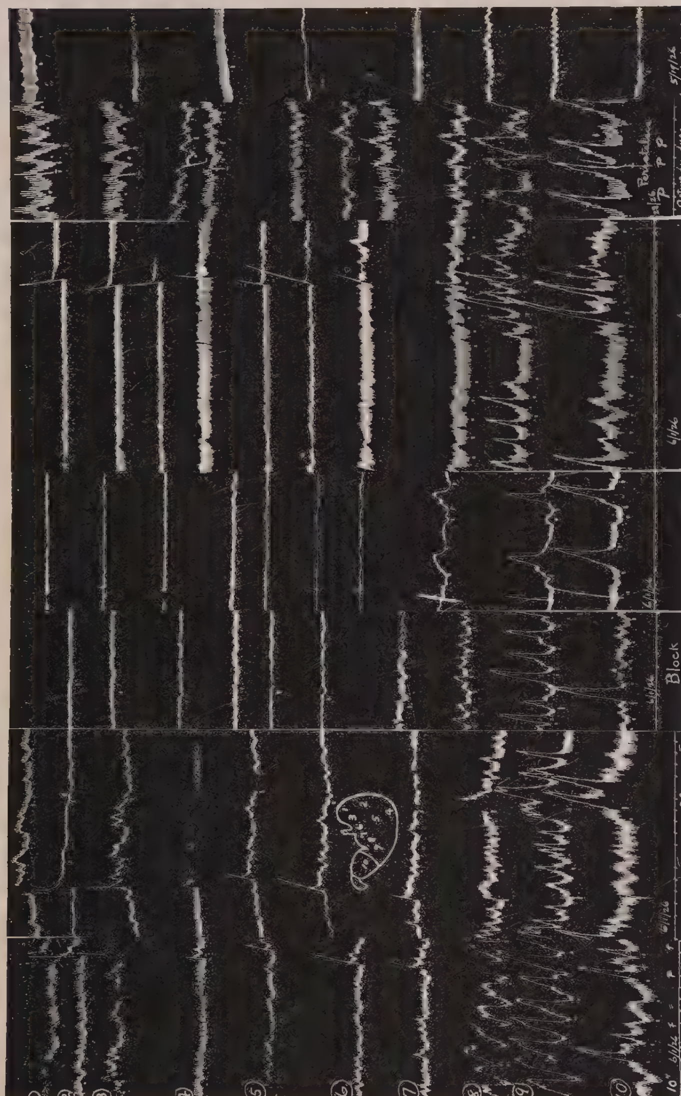

FIG. 39. Records of activity in the rabbit's stomach obtained by fastening threads to different points on the surface. The figures in the diagram, corresponding with those on the left-hand margin of the graph, show the location of the recorders. All but the last two records on the right were made from one animal. Note changes from one type of peristalsis to another. (The rapid movements are respiratory.)

waves passed over the pars pylorica peristaltically just as they did over the rest of the stomach.

In the cat, they observed about equal numbers of the two main types of contractions, the peristaltic and the systolic. Occasionally they saw pulsation in a contraction ring at the incisura when the rest of the stomach was quiet. In dogs, about 75 per cent of the waves changed into systoles at the incisura. They think that in the rabbit, dog, and man, the systolic type of antral contraction is predominant.

Klein gives a good résumé of the literature, and describes his experiments with dogs which were lightly etherized and then opened seven to ten days before they had had their vagi cut at the cardia. He saw the two main types of contraction, but variations were common. He saw ripples coming from the region of the cardia, contractions that did not move forward, stomach blocks, systoles of the tip of the pars pylorica, and occasional reverse waves running back from the pylorus and serving apparently to keep solid particles from getting into the pyloric canal. He saw also the independent contractions of the antrum which show so clearly on many of my graphic records. Incidentally, it might be noted that reverse waves in the antrum were described years ago by Haudek.

The Relation between the Experimental Findings and Peristalsis in Man. The big question now is: What relation have these findings in anesthetized, opened animals to peristalsis in normal animals and men? There can be no question now that there are many queer types of activity in the experimental animals, but are such waves ever present in healthy or diseased men and women? There are a number of observations that make me think that they are. In the first place, many of them have been seen in animals and men with the roentgenoscope and the barium meal, and little objection can be made to that technic. Furthermore, systoles of the pars pylorica were seen years ago by Auer who did nothing more to his rabbits than to shave them and watch the gastric waves through the thin abdominal wall. (Many years ago I somewhat improved this technic by first removing all the muscle so that the peritoneum was in contact with the

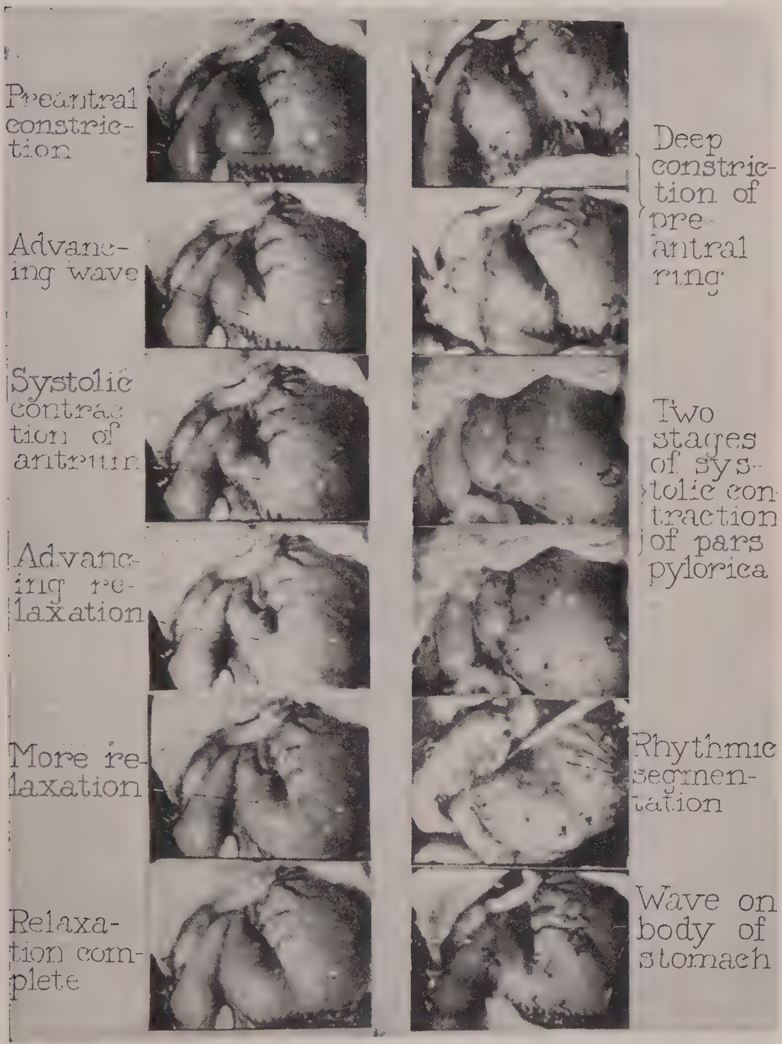

FIG. 40. Pictures of a dog's stomach reproduced from a cinematographic film. The first six on the left represent the passage of one wave over the pars pylorica.

skin.) I think also that Borchers is right in assuming that gastrointestinal motility is normal in those animals in which a celluloid window is incorporated into the abdominal wall. In cats prepared in this way he saw, for the most part, peristaltic waves going almost to the pylorus, but after every ten or twelve of these waves there was one that ended in a systolic type of contraction. He suspected that it must be this latter form of contraction which brings about emptying of the stomach.

Finally, I think we may be hopeful about the ultimate usefulness of these observations if only because practically every peculiarity that was observed years ago in the hearts of animals has since been found to have its counterpart in the heart of man, sick and well. Hence, in another twenty years we shall probably be recognizing certain syndromes which will correspond somewhat to those which we are now recognizing in the field of heart disease. Thus, we may perhaps be able to say that the desire to belch is associated with a certain type of peristalsis; the relief obtained from taking a little soda or food is due to the institution of another type; and the pain of ulcer is due to yet other types.

Some work along these lines has been done by Reynolds and McClure who roentgenoscoped patients with ulcers for hours at a time, watching to see what happened when pain came and when it went. They could find no one type of peristalsis that would always produce pain, but they did note that the onset of pain often coincided with the change from one type of peristalsis to another.

Groedel has recently spoken of peculiar waves that he has seen in diseased stomachs or in stomachs that were nearly empty. In the serial roentgenograms there sometimes are signs of disturbance in the rhythm, frequency, size, and direction of the waves that he calls "magenarrhythmie," also "kleine arrhythmische Peristaltik" along the middle of the greater curvature: small, shallow, multiple kneadings running now caudad, now orad, perhaps in the muscularis mucosae. Theile has seen what is probably the same thing in the stomachs of infants, and Palugyay (1921) has also spoken of them. I have seen them in the fundus, with patients

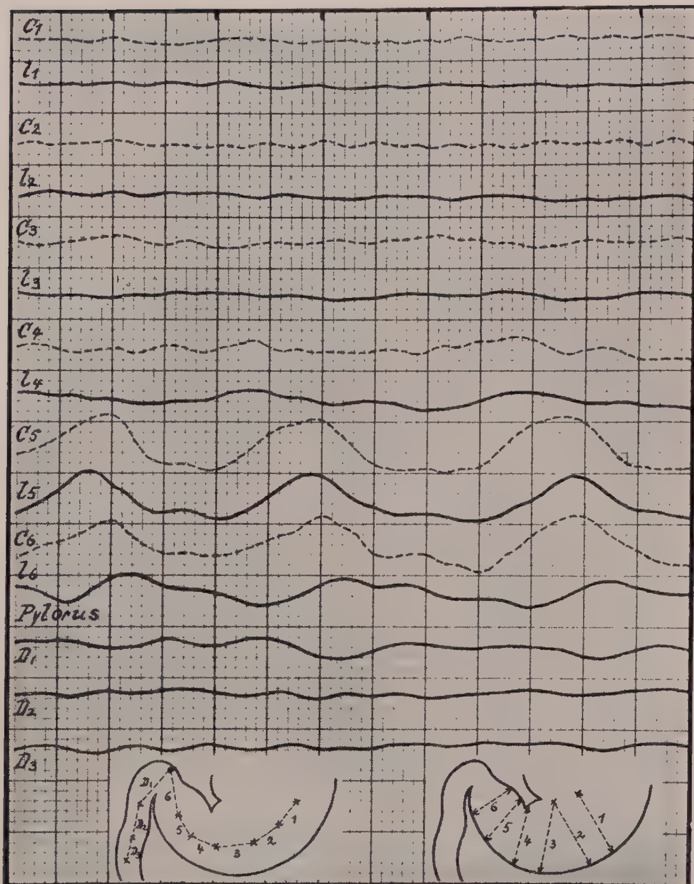

FIG. 41. The small diagrams show the location of the markers used in the analysis of motion pictures of the dog's stomach—the different diameters and longitudinal distances measured in every eighth picture in the film. These distances are plotted as ordinates with intervals of time as abscissas. The heavy dots at the top of the figure represent intervals of five seconds. The records read from left to right and a rise in the lines represents a contraction of the muscle. The heavy lines represent contractions of the longitudinal muscle and the dotted lines those of the circular. The figures on the margin at the left correspond to those in the small diagrams.

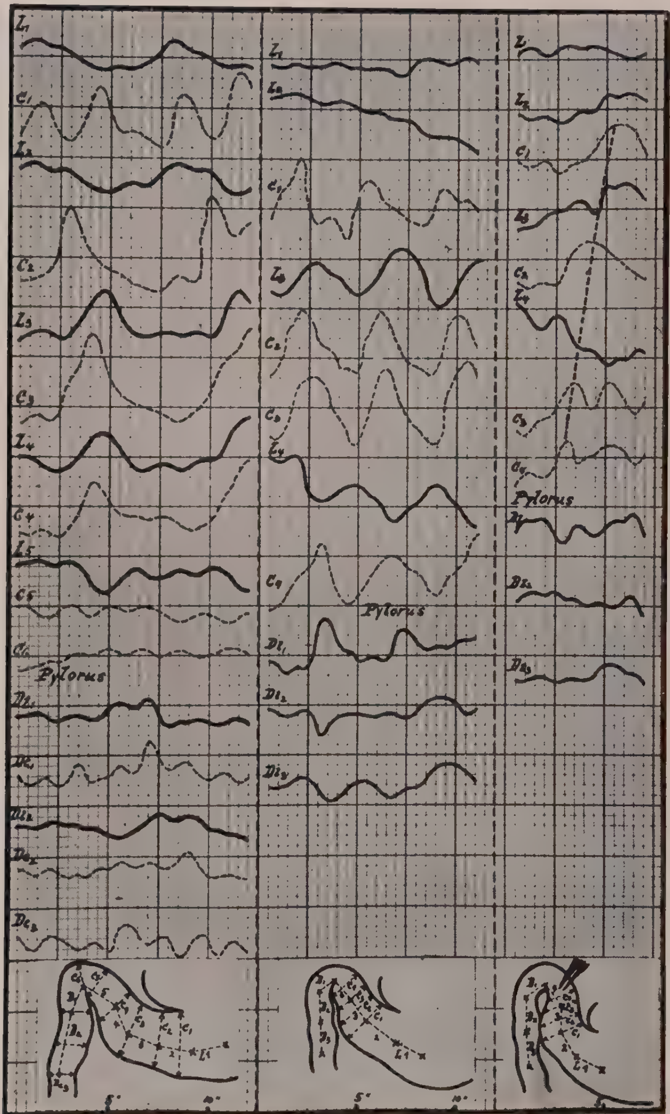

FIG. 42.—The technic of producing these tracings is the same as that described in the legend for Figure 41. In the first section on the left, note (1), the dissociation between the rhythmic activities of C-1 and C-2; (2), the appearance of small contractions of local origin superimposed on the larger

in the Trendelenburg position. They correspond probably to the rhythmic segmentations that I discovered with the galvanometer, several years ago.

Conduction in the Stomach. We still know nothing about the exact method of conduction of the wave of contraction over the stomach, and unfortunately, physiologists have not yet concerned themselves much about it; yet to me the problem seems important because in the clinic we so frequently see patients whose stomachs do not empty well in spite of an obviously patent pylorus and fairly vigorous peristalsis. On a few occasions, especially when there was ulceration somewhere in the stomach, or when tissue had been excised along the lesser curvature, I have noticed that the two sides of a wave failed to meet exactly at the pylorus and therefore tried to push food out where there was no opening. The trouble seems to be that the greater curvature is longer than the lesser, so that the wave must travel faster on the outer side of the stomach in order to reach the pylorus on time. When a V-shaped piece is taken out of the lesser curvature, this disproportion is greatly exaggerated, and as surgeons now know, the proper emptying of the stomach becomes impossible (Mayo, Judd, Stewart and Barber).

Another reason for the poor emptying of such stomachs may be the weakening of peristalsis in the part below the line of excision, and the fading out of the waves before they reach the pylorus. If a "sleeve" resection is made and a complete ring removed, all observers agree that the stomach will empty satisfactorily. Theoretically, the outer side of this

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waves; (3), small rhythmic contractions in the circular muscle immediately above the pylorus resembling those in the duodenum; (4), a systolic type of contraction both in the longitudinal and in the circular muscles of the upper pars pylorica.

In the second part of the figure note the waves of relaxation in L-2, corresponding to the longitudinal muscle of the preantral region. There is some relaxation also in L-4, next to the pylorus. Note the systolic contraction of the circular muscle throughout the pars pylorica. Associated with these contractions are some in the first portion of the duodenum.

In the third portion of the figure there is depicted the progress of a wave of reverse peristalsis which originated in a pinch given to the muscle of the pylorus.

ring should be made a little wider than the inner side. According to Klein, Borchers (1921), and others, after such sleeve resections have been made the lower portion of the stomach contracts independently of the upper half. As one would expect from the gradient theory, the lower portion contracts with a rate slightly lower than that of the upper. There may be a little question on this point, however, because so far as Cannon could see, waves traveled quite normally over the stomach after the healing of several encircling incisions which he had made through the muscle down to the mucous membrane (Cannon, 1911[d], p. 258).

Years ago, Kirschner and Mangold cut the stomach of dogs in two near the incisura, connected the upper pouch with the jejunum, and turned in the upper end of the lower pouch; they thus isolated the pyloric portion and later were able to show that it functioned quite normally. This is what we should expect not only from the studies on stomach block but from those with the excised strips; certainly the muscle in the region opposite the incisura must have a high degree of rhythmicity so that it can easily assume the function of pacemaker for peristaltic waves. It is hard to say yet how wide this strip is, but my impression is that it extends for a centimeter or two above the point where the pale muscle of the body of the stomach shades into the reddish muscle of the pars pylorica.

Some observations of Carlson (1916, p. 226) are of interest in connection with this problem of conduction in the stomach. He made in each of two dogs a Pavloff pouch, one of which was connected to the stomach by a band of muscle 6 cm. wide and the other 3 cm. wide. In the first dog, the hunger contractions in stomach and pouch were synchronous, while in the second they were not. This experiment resembles the one in which the heart beat is made to pass across narrow bridges of auricular muscle. As has been pointed out earlier in this chapter, with the motion-picture technic we are now attacking the problem of conduction and have already obtained evidence of a change in rate near the incisura.

Rate of the Peristaltic Waves. As is well known, in the stomach of man there are about three large peristaltic waves

a minute, and that holds true also for a number of laboratory animals. In the cat, there are generally five or six in a minute. According to many observers this rate is slowed when fats are eaten. A number of investigators have tried to establish some relationship between the reaction of the gastric contents and the depth of peristalsis, but without much success.

Tonal Adjustments. The stomach seems to have some means of adjusting itself automatically to the size of its contents, with the result that the intragastric pressure remains about the same with meals of different sizes. Groedel gives interesting diagrams showing the size and position of the stomach with successive mouthfuls. As was pointed out in the preceding chapter, the muscle from the fundus seems to possess a faculty of tonal change which is not shared by the muscle of the pars pylorica.

A Humoral Mechanism. That the muscular activity of the stomach can be affected by food derivatives which have been absorbed into the blood has been shown by Farrell and Ivy who transplanted a piece of dog's stomach under its skin. Within five minutes after fats were put into the stomach the movements of the transplant were inhibited.

Mode of Travel of Solids and Liquids through the Stomach. In the Herbivora there is a marked tendency for food to remain stratified as it comes into the fundus, and only in the pars pylorica does mixing and trituration take place (Grützner, 1905, and Scheunert). There is a little tendency to stratification in the stomach of man (Groedel, 1912), and there is no doubt that the mass of food in the fundus remains practically undisturbed by peristalsis. As Cannon and others have shown, its reaction remains alkaline for a long time: a point of some importance because it explains why the alkali-loving ptyalin of the saliva is able to act on the starch long enough to prepare it for the final splitting by the amylase of the pancreatic secretion. It explains also why food that is regurgitated after a meal often tastes perfectly sweet and can be swallowed again with relish.

The Gastric Furrow or "Magenstrasse." In some of the Herbivora the so-called "horseshoe sling," which runs

from the cardia down one side of the lesser curvature and up the other, contracts when fluids are swallowed, and makes a furrow through which they can pass into the pyloric portion. Waldeyer called attention to the longitudinally directed folds of mucous membrane along this furrow in man and suggested that they represent a short path for fluids similar to that which is found in animals (Fig. 43). The studies of Groedel (1912), Van der Reis, Schembra and others have shown, however, that this is not true; when semi-liquid food is given to a man or woman who is standing, it can be seen with the roentgen ray that although it tends to follow the lesser curvature for the first two or three inches, it then drops straight down to the bottom of the stomach. Furthermore, if fluids are given when the stomach is full of semi-solid food, they do not follow the canalis gastricus or Magenstrasse, but make many small channels around the mass and down to the pylorus.

Fig. 43. Shows the furrow along the lesser curvature in the contracted stomach of a dog. The greater curvature has been removed, exposing the furrow with the cardia above and the pars pylorica below. (*From Kaufmann.*)

Years ago Ernst made a statement, since often quoted, to the effect that when small amounts of corrosive poisons are swallowed, most of the destruction of the mucous membrane takes place along the lesser curvature. If this were always true, it would support the theory that liquids follow the lesser curvature, but according to Katsch and Friederich, there is little basis for Ernst's statement. The question is of some importance because Aschoff and others have claimed recently that the frequent appear-

ance of ulcers and tumors along the lesser curvature is due largely to the greater traumatization of that pathway by hot and otherwise irritating foods. There may be something in this view, but I think Cannon had more reason for pointing to the mucous membrane of the pars pylorica as the most highly traumatized part of the stomach. All of the trituration and mixing of food with gastric juice takes place there, and solid particles have to be pushed forward and backward for some time before they can get through the pylorus. Perhaps the greatest objection to all these explanations is that they fail to account for the fact that the commonest site for ulceration is just below the pylorus and quite outside of the stomach.

The Blood Vessels of the Magenstrasse and Cap. The anatomical studies of Reeves are of interest in this connection in that they showed marked differences between the submucous arteries on the lesser curvature and those in the rest of the stomach. On the lesser curvature they run in a longitudinal direction; they are small, they make few anastomoses, and they run for more than twice the distance that is covered by vessels of the same size in other parts of the stomach. It was harder, also, to get good injections of these vessels in the duodenal cap, where he confirmed Wilkie's discovery of peculiar arteries. The arrangement of the submucous vessels of the duodenal cap is strikingly different from that lower down in the bowel: the blood supply is poorer, and the arteries resemble those in the stomach. Other good studies of the gastric vessels have been made by Disse, Usadel, Jatrou, Hoffmann and Nather, and Armbruster.

Suggestive, also, in relation to the problem of ulcer are the careful histologic studies now being made of the mucous membrane of the stomach by Aschoff, Moszkowicz, Puhl, and others, showing the existence, especially along the lesser curvature, of islands of epithelium resembling that of the bowel. Another interesting point about the lesser curvature is that it is the one place in the stomach in which the mucous membrane is firmly fastened to the muscle. Its attachment is much looser in the body of the stomach, very loose in the pars pylorica, and firm again in the duodenal

cap. Many other points in regard to the anatomy and development of the stomach will be found in Chapter XII.

The experiments of Klein and others have shown that the mucous membrane along the lesser curvature is more sensitive to mechanical stimuli than that in other portions of the stomach. Irritation there is also more likely to lead to hourglass types of contraction. These contractions are not so likely to occur with lesions near the greater curvature, and according to Borchers, they do not recur if the whole lesser curvature is removed from the stomach.

The Position of the Stomach in the Abdomen. Although Glenard, in the eighties, called attention to the existence of gastroptosis, it was not until the roentgen ray came into general use for the diagnosis of gastrointestinal disease that physicians began to get alarmed over the fact that many stomachs hang down like long stockings with the lower pole in the pelvis. The picture on the fluorescent screen, with the subject in the upright position, was so different from everything that they had seen before that they thought they were dealing with disease, and felt sure that something should be done about it. Soon, however, those with a large clientele began to see that this long type of stomach must be normal, especially for the thin, frail type of individual, and so long as there was no great delay in the emptying time, they ceased to pay any further attention to the finding.

The best study of the subject has been made by Moody, Van Nuys, and Chamberlain, who picked out 600 of the healthiest students they could find at the University of California, 200 of them athletes or students majoring in physical education, and gave them each a barium meal. With the subject standing, it was found that the lowest point on the greater curvature of the stomach was below the interiliac line (drawn between the highest points on the iliac crests) in 74 per cent of the men and 87 per cent of the women. In 25 per cent of the men and 46 per cent of the women it was more than 5 cm. below the line, and in 7.6 per cent of the women it was more than 10 cm. below. Even the lesser curvature in the region of the incisura was found below the interiliac line in 13.1 per cent of the men and

28.8 per cent of the women, and in some cases even the pylorus was below the line.

These observers could not establish any constant relation between the build of the individual and the position of the stomach; the most powerfully built man and the most powerfully built woman in the series each had "gastroptosis." It suggests to me that the genes that determine the position and shape of the stomach are not always coupled with those that determine body build and muscular development. Incidentally, it should be noted that there is no such thing as a dropped stomach: the fundus never drops away from the diaphragm, so if we wish to be correct we should speak of long stomachs.

The stomach is a muscular tube like the bowel and it is hard to see why it should be affected by its position in the abdomen. The viscera and the food have all about the same specific gravity, which differs but little from that of water, so everything floats together in the abdominal cavity, and one would not expect the position of any segment of the tube to make much difference in the rate of emptying. Because of these theoretic reasons, and also because the improvement after operations is generally but temporary, most conservative surgeons have long since given up the practice of trying to fasten up the stomach or to make pleats in it; and most physicians have given up their attempts to raise its level by prescribing abdominal exercises, or blocks to be put under the foot of the bed. Many asthenics are helped by Weir Mitchell cures, high calorie diets and better corseting, but their gain in health and comfort is due probably to the rest, the better nutrition, and the increase in abdominal pressure, which may perhaps help by improving the absorption of food and gas.

The Stomach in Infants. Excellent reviews of this subject have been made by Theile (1917) and by Rogatz. The latter recognized two main anatomic types: one in which the stomach looks like a fairly long narrow pear, and the other in which it looks like a globe. Strange to say, when he gave thick gruel or mashed potato, the stomach always contracted and became more globular, and the air bubble

became very small; ordinarily at the end of a meal made up of fluids, the air bubble represents from one-fourth to one-third of the area of the gastric shadow in the roentgenogram. As will be seen in the next chapter, these observations have some clinical value because they offer an explanation for the fact that infants with congenital pyloric obstruction will often stop vomiting when they are given semi-solids. With the improvement in tone, the stomach is better able to push the food past the obstruction.

According to various observers, the emptying time of the infant's stomach varies from one to four hours. Mother's milk, half milk and malt soup leave comparatively early, while whole cow's milk and buttermilk leave rather late. As in adults, small amounts of food leave more slowly than large ones, and fats tend to slow the emptying of the stomach.

More information in regard to the roentgenoscopic findings in infants' stomachs can be found in books by Carman and by Kerley and Lewald.

CHAPTER XIV

HUNGER CONTRACTIONS AND THE PAIN OF ULCER

Boldireff (1904[b], 1914) is generally given credit for having been the first, in 1904, to note the presence of contractions in the fasting stomach, but I think it should be remembered that Morat, in 1882, recorded gastric-hunger contractions in unanesthetized dogs with the same technic that is used today. He remarked then that it would not be difficult to

Fig. 44. Anton J. Carlson.

get similar records from men and women, but he would leave that for the clinicians. Apparently they did not take up his suggestion because in 1893 he tried it himself, and obtained some good tracings. So far as I can find, he did not note the relationship of the contractions to the pangs of hunger; that was left for Cannon and Washburn to do in 1912. To be sure, Haller states in his "First Lines of Physiology" (p. 313) that hunger is due to the rubbing together of the folds of the stomach, but credit cannot be given him for this until some historian assures us that it was based on observation and not, like some other of his statements, on philosophic reasoning.

Considerable credit can be given to Schwartzenberg who, in 1849, commented on the hunger contractions that he saw in the ileum of a dog with a fistula; to Busch who, in 1858, saw them in the empty small bowel of a woman who had been gored by a steer, and to Rossbach (1890[b]) who saw them in the bowel of a woman with a large thin-walled hernia. Busch's patient was ravenously hungry all the time because her food ran out through a high jejunal fistula, and he thus was able to differentiate the two factors in hunger: a demand for food

FIG. 45.—Andrew C. Ivy.

on the part of the tissues, and a sensation arising in the digestive tract. Rossbach came close to our present conception of hunger when he remarked that in connection with strong hunger-feeling the bowel always showed unusually lively peristalsis. He gives references also to the papers of many of the older workers who saw contractions in the empty stomach (p. 698).

In 1912 Carlson and his pupils began the long series of studies that have since thrown light on almost every phase of the hunger mechanism, and have given us the monograph on

the "Control of Hunger in Health and Disease": a storehouse of information in regard to hunger, appetite, the sensibility of the gastric mucous membrane, and the relation of the digestive tract to the nervous system.

According to Carlson, when a recording balloon on the end of a Rehfuss tube is put into the stomach of a fasting man, the tracings made on the kymographic drum will generally show alternating periods of quiet and activity. After a period of rest which may last for from one-half to two and one-half hours, the first contractions will probably appear at intervals of from two to five minutes; these intervals shorten, the contractions become more powerful, and finally there may be short periods in which the stomach remains contracted. In a strongly built man, the cycle of activity usually lasts for from thirty to forty-five minutes. The feeling of hunger seems generally to be due to the waves which come about every thirty seconds. Sometimes these waves and other small ones with a period of twenty seconds are superimposed on slow tonus waves which last from one to three minutes. More rarely there is an atypical form of hunger activity in which there are no definite periods of contraction and rest, and in which the individual waves are irregular both as to strength and time of appearance.

In dogs there are at least three types of hunger activity, depending on the tone of the stomach. In the first type the tone is poor, the contractions last about thirty seconds and the intervals between them vary from a half minute to four minutes. These contractions come in groups and keep recurring for from a half hour to three hours. In the second type the tone of the stomach is good, and the contractions follow one another in close succession. They are frequently interrupted by periods of incomplete tetanus lasting for from one to five minutes; the contractions then do not come in distinct groups, but are practically continuous. This type has been seen occasionally in man, and it results in a continuous sensation of hunger. In the third type there are periods in which there is a tetanic type of contraction, with a series of rapid contractions superimposed. These periods vary in length from one to ten minutes.

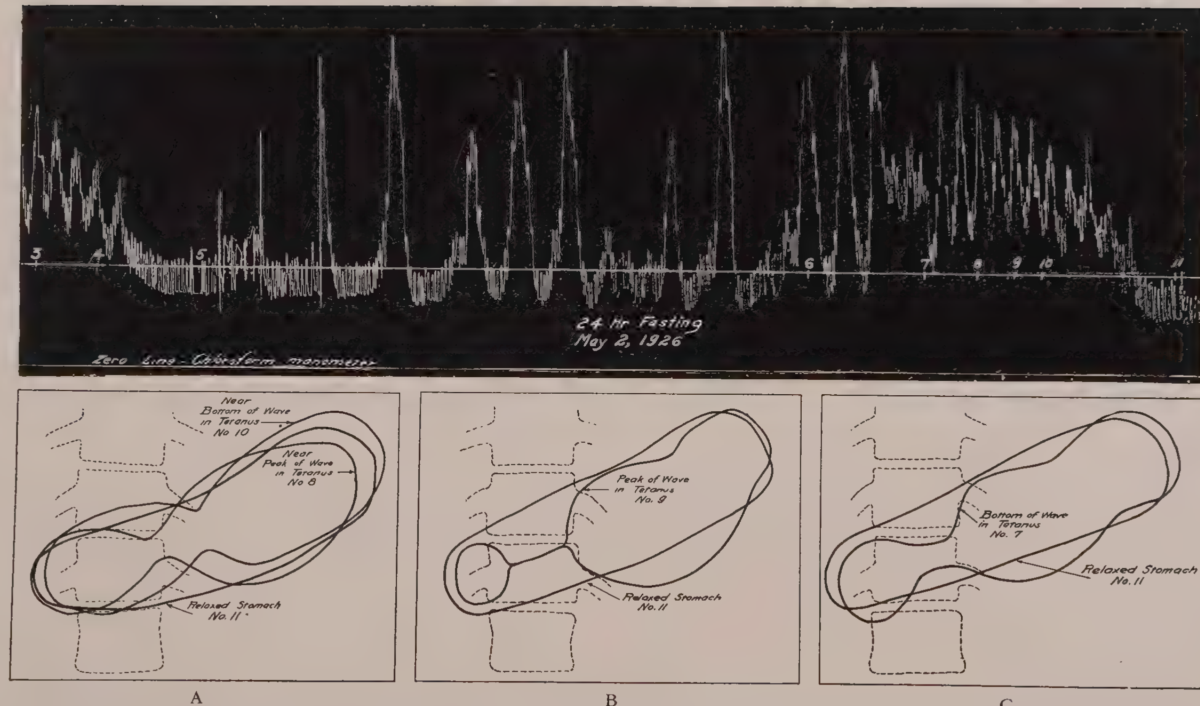

Fig. 46. Kymographic tracing of hunger contractions together with tracings (from roentgenograms) showing the shape of the stomach (A) during partial tetanus, (B) during the peak of a contraction wave superimposed on partial tetanus, and (C) at the bottom of a contraction wave during partial tetanus. (*From Martin and Rogers.*)

Contractions felt as hunger pangs may appear when the stomach still contains traces of food. By watching the balloon with the roentgenoscope, Carlson could see that the hunger contractions were actual peristaltic waves coursing from one end of the stomach to the other. Sometimes they shaded over into the ordinary digestive waves, but usually they were not only more intense but somewhat different in character. They began high up near the cardia and involved the whole stomach, while, as is well known, the digestive waves are most marked in the pars pylorica. More recently Martin and Rogers made roentgenograms of the intragastric balloon during the progress of hunger contractions and observed deep constrictions only in the pars pylorica. These constrictions moved caudad a short distance and at the same time there was often some shortening of the whole gastric shadow.

As is well known, the taking of a little food or soda often causes hunger distress to disappear, and this suggests that an abnormal type of gastric peristalsis has also ceased. Actually, as will be seen later, one of the most characteristic features about the hunger contractions is the way in which they are inhibited by the taking of food or alkalies; according to Rogers and Hardt, they are more susceptible to inhibiting influences than are the digestive waves.

Inhibition of the Hunger Contractions. The hunger contractions can be inhibited for a time by having the subject taste various foods or drugs, by having him chew palatable or even indifferent substances, and sometimes by having him swallow. They are not always inhibited by the presence of food-metabolites in the blood because they start up sometimes when absorption is still taking place from the bowel. An emptiness of the stomach alone, however, will not always bring on hunger pain, as can be shown by washing out the gastric contents during the course of digestion.

The pains are inhibited for some time after the giving of water, dilute alcohol, dilute hydrochloric acid, alkalies, and food, but are only slightly affected by the presence of air or carbon dioxid. They are inhibited also if some gastric juice or dilute hydrochloric acid is introduced into the bowel. These long-distance effects persist after section of the vagi

and splanchnics, but the latent period is longer, the degree of inhibition is less, and the effects are more transient. The same observations have been made in the case of other inhibitions of the digestive tract, all suggesting that the usual pathway is along nerves in the mesentery, and that when these are gone, the impulses must travel slowly through Auerbach's plexus.

Smoking will cause some inhibitions of the hunger contractions if the mucous membrane of the mouth is sufficiently stimulated as by a "biting" pipe. Tightening of the belt, contrary to what one might expect from popular belief, does not inhibit the hunger contractions. The effects of a number of drugs on the mechanism have been well studied by Ginsburg and Tumpowsky (1918). According to Carlson, Van de Erve, Lewis, and Orr, the bitters commonly used in medicine with the idea of increasing appetite have no effect on the hunger contractions, except perhaps a depressant one. It should be noted, incidentally, that appetite and hunger contractions do not always go together. The hunger contractions may disappear entirely during the course of infections, such as common colds.

THE PAIN OF ULCER

Although the hunger pain of peptic ulcer constitutes one of the most striking symptoms met with in daily practice, its origin is still problematic, and the many curious facts about its coming and going still remain largely unexplained. Two main theories have been offered: one that the pain is due to deep muscular contractions, and the other that it is due to an increase in the acidity of the fluids bathing the ulcer.

Particularly in the case of duodenal ulcer without obstruction at the pylorus, some explanation for the early appearance of strong hunger contractions, usually within two or three hours after the taking of food, may be found in the fact that the emptying of the stomach is generally much accelerated (at least at the beginning of digestion).

One of the earliest studies on the sensitiveness of the stomach to acids was made by von Pfungen and Ullman who, in

1887, put 0.3 per cent hydrochloric acid into the stomach of a boy with a gastrostomy opening, and produced pain in the epigastrium, and headache. They could see little change in the activity of the stomach until they put in some alkali which increased the number and depth of the gastric waves and at the same time relieved the child's discomforts.

In 1916 Ginsburg, Tumpowsky, and Hamburger reviewed the literature on this subject of gastric pain, and studied 10 ulcer patients with the balloon technic. Their impression was that the pains were associated with hunger contractions. Carlson (1917) came to the same conclusion from studies on a student with ulcer. As the contractions were not unusually deep or powerful in their cases, Carlson and his students felt that the change from a normal hunger distress to a pathologic hunger pain must be due to an increase in the sensitivity of the nerve-endings.

Hardt (1918, 1922) studied a number of ulcer patients with two tubes running into the stomach, one to record the contractions and the other to secure samples of the gastric juice. He concluded that there was a relation between the pains and the contractions of the stomach, but none between the pains and the degree of acidity. Some patients complained of pain in spite of the fact that at no time did they have any acid in the stomach; and still more surprising, they obtained relief when their stomachs were washed, or when they were given alkalies. Crohn and Wilensky made similar studies but were not so sure about a relation between the pains and the contractions. They found that there were no contractions in about a fifth of their ulcer patients, and in many others the tone of the stomach was poor.

Palmer's results were similar. A study of several hundred tracings showed that in most instances the tone and motility of the stomach were decreased during the periods of ulcer distress (1926[b], 1927). The tone rose when he stopped the pain either by removing the contents of the stomach or by injecting eggnog or alkalies. The tone and activity of the duodenum varied as did that of the stomach. He gave an acidulated barium meal to 30 patients with ulcer and 30 normal controls, and saw nothing distinctive about the type

of gastric peristalsis present during the periods when pain was felt. He concluded, therefore, that in about 90 per cent of the patients the chemical irritant was the only factor in the production of distress; in the remaining 10 per cent muscular contraction may have had something to do with it.

Ortmayer, also working in Sippy's clinic, could not satisfy herself of a definite relation between the hunger contractions and the pains. When her patients were distressed she gave them large doses of alkali, and although they were always relieved, there was seldom any definite change in the appearance of the kymographic record. Homans had similar negative results: sometimes there was great pain without contractions, and at other times there were deep contractions without pain. He admits however, that his recording balloon was in the body of the stomach, so he could not rule out the presence of cramplike contractions at the pylorus. In a number of his patients he made the interesting and not easily explainable observation that at times the simple turning from one side to the other was enough to stop the pain. Poulton found that in the presence of an ulcer, pain can often be produced by distending the stomach with air, and relieved by passing a stomach tube. Some ulcerated stomachs do not respond to the test, and conversely, the production of pain in a subject does not mean necessarily that an ulcer is present.

Palmer (1927), who seems to have made the most extensive study of this subject, found on 19 occasions a definite association between intense peristalsis and pain, but in 198 other experiments there was pain without any sign of unusual gastric activity. Although, as will be seen later, he is inclined to the view that the acid is the more important factor, he admits that powerful contractions may at times have an influence. Using an acidified barium meal, he was unable to see anything unusual in the gastric and duodenal peristalsis of 48 patients with ulcer, and similar, largely negative, results have been reported by Reynolds and McClure. Wilson has noticed in many patients that the pain lets up the moment chyme passes through the pylorus.

The presence of an ulcer type of pain in some cases of carcinoma of the stomach is hard to explain because the acids are often very low, and the base of the lesion is so dense that the waves of peristalsis cannot run over it.

Hunger Contractions outside the Stomach. One of my main objections to Carlson's original explanation of hunger pain in patients with ulcer is that, in most cases, the lesion is situated below the pylorus where it can hardly be pressed on by the gastric contractions. In the last few years, however, the studies of Wheelon and Thomas (1920, 1921 and 1922), Alvarez and Mahoney (1923), Payne and Poulton, and Ivy and Vloedman have shown that the tone of the duodenum not infrequently rises and falls with a rhythm similar to that of the stomach, and often fairly closely in phase with it; and according to Payne and Poulton, and Ivy and Vloedman, the hunger pains not infrequently are timed more closely with the contractions of the duodenum or jejunum than with those of the stomach. This pain could be produced even in patients with ulcers insensitive to acid, and it was often felt in the epigastrium where the usual ulcer pain appears. Payne and Poulton's careful study of the hunger contractions in the esophagus suggests that some of the pain of ulcer is produced by spasm in that tube.

Summary of Evidence for the Mechanical Theory of Pain Production. It appears, therefore, that although the various workers with the ballon technic do not agree, they have gathered some evidence to show that the pains of ulcer are related to hunger contractions. Unfortunately they do not seem yet to have faced the question why the hunger contractions cause pain when the unusually deep and powerful digestive waves, so commonly seen with ulcer, are actually soothing. One fact emerges quite clearly: that the essential feature in the production of pain is not an increase in the depth of the hunger contractions but an increase in the sensitiveness of the nerve-endings. This point should be noted particularly because it will be discussed again in the review of the work on the effects of acid on the ulcer pain.

One question that troubles those who believe in the hunger contraction theory of pain is: How often is the distress of

ulcer intermittent enough to be caused by the usual type of rhythmically recurring hunger spasms? Although for years Carlson has been asking this question of his clinical brethren, I am quite sure that he has not yet had a convincing answer. Patients themselves cannot always tell, even when they are intelligent and observing. If the pains should be found generally to be non-rhythmic in character, the hunger contraction explanation would become less attractive although it would not be ruled out. There probably are two types of hunger pain just as there are two types of hunger contraction.

THE PRODUCTION OF PAIN BY ACID

To the average practitioner of medicine it must seem obvious that the pain of ulcer is due to the acidity of the gastric contents because it can be relieved so easily by the giving of alkalies. In favor of this view also is the fact that a few investigators, notably Heineke and Van Selms, Bönniger, Talma, Suyling, and Palmer (1926[b], 1927), have been able to increase the distress of patients with active ulcer by putting into their stomachs, through a tube, considerable amounts of dilute hydrochloric acid of a strength usually about twice that of the normal gastric juice.

Against these observations must be set those of a number of other workers (Hurst, 1910, p. 101, Hurst, Cook, and Schlesinger, Löwenthal, Schmidt, Boring, Bönniger, Ginsburg, Tumpowsky and Hamburger, Carlson and Braafladt, Zimmermann, and Schür), who, in most or all of their subjects, with and without ulcer, failed to produce anything but a slight burning sensation. Against the theory of acid-causation is also the fact that many workers have failed to detect any correlation between the presence of pain and high acidities either in different patients or in the same patient at different times. Many persons with ulcer have normal or low acidities but that does not render them immune to pain, and even those with no free acid have pain. Although as Palmer (1926[a]) points out in his review of the literature on this subject, many of the achlorhydric patients were not studied as carefully and repeatedly as they should

have been to establish their status beyond question, there is no doubt that many of them, for much of the time, had no free acid, and that is enough to back up the argument.

There are many patients also with carcinoma or syphilis of the stomach and little or no free acid but with pain that cannot be distinguished from that of ulcer with hyperacidity. It is interesting also that when cancer develops in the wall of an old ulcer, the amount of acid in the stomach generally drops, but the pain often grows worse and becomes more constant.

Against the theory of acid causation is also the fact that a little soda will bring relief from pain when fractional analyses show either that the acids were low to begin with, or else that after a momentary drop they returned to a high level. Furthermore, prompt relief can often be obtained by the taking of a little food which cannot combine with much acid and which may even lead to the production of more than there was to begin with, and sudden remissions of pain will come in the absence of treatment, or when the patient takes to his bed or goes on a vacation. As Sippy has said, "the pain of ulcer may be entirely absent when the aspirated stomach contents show even high grades of free hydrochloric acid."

The immediate and usually permanent relief that comes with the making of a gastroenterostomy is also puzzling because as will be pointed out in Chapter XVI, it cannot always be explained on the basis of a drop in the acidity of the gastric contents. Even stranger is the complete disappearance of symptoms that often comes simply because the ulcer has bled profusely.

Fortunately, much of the old tangle of conflicting evidence seems to have been straightened out recently by Palmer. He finds as Talma did away back in 1884, and as Bönniger did in 1908, that the stomach of a patient with ulcer may be sensitive to acid on one day and not on another: everything depends on the state of irritability or activity of the ulcer. If the mucous membrane is normal, or if an ulcer has healed or has become symptomless, the subject will rarely feel the presence of from 100 to 200 c.c. of 0.5 per cent hydrochloric acid; but if the ulcer is active and giving symptoms, the

administration of the acid will generally bring on an attack of typical pain, and its neutralization or removal will bring relief. That some other, as yet unknown, factors enter into the problem, however, was shown by Palmer's failure to produce pain in a small group of patients with active ulcer.

The theory that pain is produced by an increase in the acidity of the stomach thus receives great support, but it must not be forgotten that many things remain unexplained. Why, for instance, does hunger pain, or something that clinicians cannot yet distinguish clearly from it, appear occasionally in patients in whom, at operation or necropsy, the stomach and duodenum seem normal? It may be, perhaps, that a diseased gallbladder or appendix has sensitized the nerve endings in the stomach, or possibly in some cases a shallow ulcer was overlooked.

I have, however, seen several patients, and my friends have told me of several more, in whom there could be little doubt about the association of typical ulcer pain, relievable by alkalies, with an unbroken mucous membrane in stomach and duodenum. Recently Judd and Nagel have found that in some of these cases the lesion is a duodenitis. Dr. Winkelstein has told me also of the case of a syphilitic girl with hunger pain for a year, relieved by food. There was a complete achylia. As she did not improve on antisyphilitic treatment a subtotal gastrectomy was done and it was found that there was no defect in the mucosa; the small gummas, the vascular changes, and the scarring were mainly in the submucous coat. The operation gave complete relief from symptoms. In a somewhat similar case observed at the Mayo Clinic, the specimen showed a granulomatous change in the mucous membrane of the stomach due to the tubercle bacillus, and again there was no ulceration.

The clinical picture of ulcer, with typical pain, can be produced in middle-aged persons by cancer of the stomach; and hunger pain, coming at 11 A.M., 4 P.M., and 1 A.M., but not definitely relieved by food, is seen occasionally with old chronic ulcers, with carcinomatous ulcers, and with lesions of the lower ileum or upper colon. I have seen it with chronic

amebiasis. Apparently the pain comes when the lower ileum finds it difficult to force its contents past an irritable place. The taking of more food gives relief probably because it adds enough *vis a tergo* so that the material in the bowel can move forward.

In some cases of carcinoma Palmer (1927) was able to produce an ulcer type of pain by introducing acid into the stomach, and just as with the benign ulcers, so here, he was able occasionally to desensitize the patient with the help of a "Sippy cure." There were a few cancer patients with fairly normal acids who obtained relief from pain with alkalies, and one with practically no acid who was completely relieved from pain when the stomach was washed with cold water. The pain could also be relieved by the taking of food, which suggests that it must have been due to muscular contractions because it could hardly have been due to hydrochloric acid. In other cases of cancer the pain was so constant and so intractable that Palmer suspected that nerves had been infiltrated or injured in some way. This theory has been discussed also by Perman.

Ivy's Theory. Some unpublished observations of Ivy, which he has generously permitted me to mention here, throw light on the nature of the sensitizing process. He finds that in the dog, as in man, the normal bowel at the mouth of a Thiry fistula is not sensitive. It may be clamped or cut without giving rise to any complaint; but when the mucous membrane becomes everted, edematous, and congested, it cannot be pinched without giving rise to great pain and sometimes to vomiting. Somewhat similar observations were made years ago by Kast and Meltzer. Ivy has noticed also while working on Pavloff pouches that if fluids are injected into the submucosa, so as to lift the mucous membrane away from the overlying muscle, pain will sometimes be produced.

Ivy believes that the intermittent type of ulcer pain is due probably to changes in the tonicity of the muscle at the site of the ulcer, brought about by peristalsis or local spasm. The continuous type of distress is due to congestion, edema, and inflammatory reactions about the ulcer, all of which lower the threshold for stimuli. The acid plays a rôle because

it irritates the nerves and increases the edema about the ulcer. He agrees with those who believe that the lowering of the threshold is an important factor. Apparently in some patients it becomes permanently lowered, so that the pain continues even after the ulcer is removed.

SUMMARY

It seems to me that all we can conclude from the work reviewed is that the main factor in the production of ulcer distress is a sensitization of nerve-endings in the upper part of the digestive tract: a sensitization that causes them to respond painfully either to the presence of acid or of certain types of contractions in the stomach, duodenum, or esophagus. When the nerves become less sensitive, the threshold is raised and the ulcer ceases to cause symptoms. Unfortunately, this explanation leaves many puzzles unanswered, and it probably does not add much to our real knowledge of the subject. The discussion will help greatly, however, if it serves to remind us, as Josh Billings would say, that it is better not to know so much than to know so many things that aren't so.

One of the lessons to be learned by the clinician from the work on hunger contractions is that he cannot put the stomach at rest simply by withholding food. Actually, in the presence of an ulcer, the powerful hunger contractions are much more disturbing and probably more harmful to the patient than are the waves that course over the lower end of the stomach during the periods of digestion; and certainly, one of the easiest ways in which these patients can be kept comfortable is by giving them something to eat every two hours (Alvarez, 1926).

CHAPTER XV

THE MOVEMENTS OF THE STOMACH THAT IS DISEASED OR THAT HAS BEEN OPERATED ON

Gastric and Duodenal Ulcer. In the presence of gastric ulcer, peristalsis may be weak, exaggerated, irregular, absent or reversed. Vigorous peristalsis is more likely to be seen with ulcers obstructing the outlet of the stomach. We do not yet know enough about the ways in which ulceration affects peristalsis and the conduction of waves over the stomach. Why, for instance, do gastric ulcers situated at some distance from the pylorus often interfere with gastric emptying? It may be due to a change to a less efficient type of gastric wave or there may be a general rise in tone of the stomach which shows itself mainly as a spasmodic contraction of the particularly sensitive sphincter. There is always the possibility too that in some of these cases another ulcer has developed near the pylorus. Ulcers in the duodenum often produce a hypertonicity of the stomach and a hypermotility which is characterized by the presence of five or six deep waves coursing at one time over the stomach. The stomach tends also to empty too rapidly during the early stages of digestion and too slowly during the later stages.

Carcinoma of the Stomach. In carcinoma the waves are often shallow and infrequent. Sometimes they can be seen to approach the area stiffened by the presence of tumor cells, to skip it, and to take up their course again beyond. Reverse waves are seen occasionally, especially when there is obstruction at the pylorus; they often appear when at the same time there are normal waves going toward the pylorus.

The Stomach of the Asthenic and the Neurotic. There is nothing characteristic about the stomach in these patients; some are flabby and show only a few shallow waves, while others are markedly hypertonic, and show even a greater number of deep waves at a time than are seen ordinarily in cases of duodenal ulcer.

The Effects of the Removal of Portions of the Stomach upon Its Motility. Following the Billroth I type of operation, in which a section of duodenum and pars pylorica is removed and the two openings brought together, Case has found that in spite of the shallowness of gastric peristalsis, the emptying of the stomach is often too rapid, so that all the food may be out in from fifteen minutes to an hour. In other cases, the rhythmic segmenting movements of the duodenum come to the rescue, and the emptying time approaches normal.

In performing the various types of pyloroplasty, with excision of duodenal ulcer, the surgeon apparently does not have to be afraid of making too large an opening because the main trouble, especially in the first few weeks after operation, when suture lines are still irritable, is a failure of the stomach to empty completely. After a while this function generally improves, and according to Carman, the emptying time is eventually shortened.

After annular resections the stomach is smaller and the part below the suture line often atrophies or contracts. The line of suture is generally marked by some hourglass deformity which does not disappear under the influence of atropin. The peristaltic waves are shallow, and according to some observers, do not cross the suture line. Case (1925), however, has seen them proceeding along both curvatures all the way to the pylorus. Redwitz has made an extensive study of the results of sleeve resections in animals, and his ninety-page article, with its large bibliography, is a mine of information on the physiology of the stomach that has been operated on.

Ivy tells me that in making Pavloff pouches in dogs one must be careful to start the incision on the greater curvature above the preantral region. If one cuts too near the pars pylorica, the animals will sometimes vomit unceasingly until they die. So far he has been unable to see why this accident should happen, but he suspects that a similar sensitiveness of this region in man might account for some of the instances in which patients do badly after the making of a gastroenterostomy. The disturbance does not seem to be due to irritation of the preantral band because in the Pav-

loff-pouch dogs there is no vomiting in those cases in which, on account of careless suturing, a large ulcer develops at the point where the lower end of the gastric flap was cut away.

The results of the Mayo-Polya type of partial gastrectomy have been very satisfactory; the emptying time of the stomach is generally somewhat reduced; and as one would expect, the peristaltic waves over the gastric remnant are shallow. There is no evidence of dilatation of the loops of jejunum below the stoma.

At present there is much discussion going on as to the wisdom of doing this operation for the cure of duodenal ulcer. There are certain neurotic persons who tend to come back after a gastroenterostomy with high gastric acidity and often a gastrojejunal ulcer, and when this is removed, they may return with an ulcer somewhere else. Hence it is that many surgeons are now trying to get rid of the hyperacidity by removing the lower third or half of the stomach. Actually they often do get rid of most of the acid; and the next question is: How is it done? Why should the removal of an area of mucous membrane in which absolutely no acid is formed (Ivy 1921, and others) lessen the secretion in the glands of the fundus?

The subject has been well discussed by Portis and Portis who found in dogs that after a subtotal gastrectomy there is no free acid, but a high total. That this is due to neutralization and not to a change in the secretory activity of the gastric glands was shown by the fact that normal amounts and concentrations of acid were secreted by a Pavloff pouch in one corner of a Polya stomach.

Realizing that Ivy has done more than anyone else to separate fact from fancy in the field of gastric hormones I turned to him for an explanation of this lowering of acidity with partial gastrectomy, and here is the substance of his answer: 1. The more rapid emptying of the stomach shortens the time in which the food is in contact with the gastric mucosa, and, therefore, lessens the intensity of that stimulus. 2. The decrease in the size of the stomach may lessen the intensity of the stimulus to secrete, and some of the acid-

forming mucous membrane may also be lost at the time of the excision. 3. The cephalic part of the secretory stimulus may be lessened on account of unpleasant sensations arising in a bowel that is overly distended and irritated. 4. The stimulus to secrete that normally comes from the active bowel is delayed because the latent period is longer for undigested food than for food that has been partially digested in the stomach. 5. The stomach empties more rapidly so that acid does not accumulate as it does in the normal, or more particularly in the obstructed, stomach. 6. There may be a greater reflux of alkaline buffered secretions from the bowel. All these factors working together could account for the lowering of secretion and the masking of the acid that has been poured out.

The Complete Removal of the Stomach. One of the main functions of the stomach is to save the bowel from being overwhelmed suddenly with too much food, much as the fundus saves the pars pylorica from the menace of a peak load. Although the technical difficulties of a total gastrectomy are very great, practically the whole stomach has been removed several times both in animals and in man. In many cases part of the cardiac funnel has had to be left. One of the best known studies of the intestinal chemistry after such an operation on a dog is by M. Ogata. Luciani gives an entrée to the older literature on the subject, and some discussion of it will be found in the article by von Redwitz and in Rost's book. A large bibliography can be found, of course, in the index catalogue of the Surgeon General's Library.

Cohn's case of a woman without a stomach was discussed briefly in Chapter v. In that woman the progress of food through the bowel seemed to be slowed. E. Schwartz has described 2 cases in which he found a somewhat dilated esophagus with a gas bubble in it. The progress of food through the bowel was apparently normal, and roentgenograms showed only a little dilatation of the first portion of the duodenum.

W. J. Mayo (1923) has reported a case in which the man was well enough to work and support his family. He had

to take food at frequent intervals, and had a peculiar pallor suggesting the presence of pernicious anemia. In another case from the Mayo Clinic reported by Hartman, the patient continued to have heartburn, epigastric pain and marked salivation. He was able to take three fair-sized meals a day and milk in between. His bowel movements were loose. Two years later he developed a rather severe anemia with a color index between 1.2 and 1.6. He died about a year later and, unfortunately, a necropsy could not be obtained. On looking through the literature Hartman found another case described by Moynihan in which after total gastrectomy, the patient died with what seemed a primary type of anemia.

Mann tried to reproduce this condition in animals, but without success. He tells me that he has 5 or 6 dogs still living from which, several years ago, he removed every bit of stomach. They are in good condition, not at all anemic, with good appetites and normal bowel movements, and there is little difficulty in feeding them. They cannot, however, take as rough a diet as is tolerated by normal dogs, and they vomit if given a cereal mush containing bran, which is well digested by normal animals. Ivy tells me, however, that a severe anemia was the cause of death in several dogs in which he short-circuited the stomach and left it as a pouch opening to the outside. The animals were fed on milk, bread, and finely chopped meat. Strange to say, raw meat appeared undigested in the feces within a few hours after it was eaten, and when it was mixed with a little barium it could be seen in the colon within thirty minutes. Cooked meat was digested more satisfactorily, but in order to maintain the nutrition of his animals he had to give large amounts.

The Effect of Removing the Lesser Curvature. Borchers (1922), A. Strauss, Bauer, and Halperin have recently reviewed some of the considerations that have led a number of surgeons to try to remove the whole ulcer-bearing area along the lesser curvature. According to Borchers, when the operation is well done in man, so that little cicatricial contraction results, peristalsis is satisfactory and gastric emptying normal. In cats peristalsis is shallow and

the emptying perhaps a little faster than normal. Since 1915 Strauss has been doing this operation on patients with ulcer, and has had good results in practically all of his 21 cases. The published roentgenogram of the stomach of his first patient looks much like that of a normal man. Four patients show some hourglass contraction, but in all of them the stomach empties rapidly.

In dogs he first removed a large section of the pyloric muscle and showed that the emptying time of the stomach was shortened by about one-half. Then he removed the lesser curvature, and found that the emptying time had been lengthened a little. Shallow waves of peristalsis were seen along the lesser curvature. In some animals he removed the nerves along the lesser curvature and in others he left them, but he could not see that it made any difference in the emptying of the stomach. When he removed the lesser curvature without first taking a piece of muscle out of the sphincter, he found that the emptying time of the stomach was slightly longer than normal. The animals lived for some time in good health.

It appears from all these experiments that there is nothing about the lesser curvature like a bundle of His to make it indispensable to the proper functioning of the stomach. The amount of change seen in gastric peristalsis after these operations might perhaps have been produced just as well by long incisions and scars made between the curvatures.

According to Borchers and Kaplan the removal of even small sections of the greater curvature leads to the production of a rapid emptying of the stomach, but this has been questioned by von Redwitz (p. 549). Rapid emptying was produced also when Kaplan converted the stomachs of dogs into two pouches joined by a narrow tube along the lesser curvature. The serial roentgenograms made by Groedel in cases of hourglass contracture in man show that sometimes the waves travel quite normally over the lower sac, while at other times they are shallow or do not run over the pars pylorica at all.

Dagaew, Kaplan, Strauss, Kreidl and Müller, and others have shown that the removal of the pyloric portion of the

stomach causes a slowing of the progress of material through the bowel. The strong antral muscle seems to act like a pump to send the material forcibly on its way. The studies of Ivy on the motility of the stomach and bowel in dogs, in which gastric and duodenal ulcers had been made, revealed much the same deviations from normal as are seen in man.

CHAPTER XVI

THE MODUS OPERANDI OF A GASTROENTEROSTOMY

The pioneers in abdominal surgery had a good deal of trouble with gastroenterostomies that did not work satisfactorily. In many cases the stomach would not empty, and in others there was instituted what came to be called a vicious circle; that is, material would apparently leave the stomach through the pylorus and return through the stoma, or vice versa. As Fowler once pointed out, there never was any doubt about the viciousness of the process, but there always was some question about its being a "circle." In their efforts to avoid this trouble many surgeons contributed improvements to the technic of the operation and by 1906, W. J. Mayo could report that in his experience this complication had practically disappeared.

Apparently much of the trouble in the early years was due to the twisting of the rather long loop of jejunum that surgeons had been in the habit of using in order that they might make the gastroenterostomy with the direction of peristalsis the same in stomach and bowel. After this danger was recognized, it became the practice at the Mayo Clinic, and in many other surgical centers, to use a short loop, from 1½ to 3 inches long, and to place the stoma near the greater curvature in such a way that the jejunum keeps its original direction from the ligament of Treitz toward the patient's left. As a result, the direction of peristalsis in the bowel is opposed to that in the stomach, but that does not seem to make any difference in the functioning of the gastroenterostomy.

Figure 47 will, I think, make this clearer than any amount of verbal description. It shows the gastroenterostomy as it would appear if the stomach and mesocolon were transparent. Care must be taken of course to see that the proximal loop of the jejunum is not too short as then it is likely to bind the stomach to the spine and produce kinking.

Dr. Balfour tells me that today, although this technic is closely followed at the Mayo Clinic, it appears that the

direction of peristalsis in the jejunal loop cannot be so important as was originally thought, because many surgeons are getting good results with gastroenterostomies in which the jejunal loop is turned to the patient's right. Furthermore, Moynihan reports excellent results with the stoma placed transversely across the stomach, or parallel with the spine. Doubtless success depends on skillful handling of many details in the technic and on good judgment in deciding on the proper length of the loop. It is now recog-

FIG. 47. Shows a gastroenterostomy as usually performed. *(From W. J. Mayo.)*

nized that the stomach often hangs very low and this point is being taken into account. Figures 49 and 66, taken from an article by Van der Reis and Schembra, give an idea of the relative positions of the greater curvature of the stomach, the first loop of the jejunum, and the transverse colon.

Theoretically, on account of the prevailing direction of gastric peristalsis, it would seem wise to make the opening as near as possible to the pylorus, and Hartman and others have reported good results following this practice. In the experience of most men, however, this type of operation has not worked well, and almost everyone now is careful not to make the stoma either too near the pylorus or too far up

on the fundus. The best place seems to be at the most dependent point of the stomach which, as W. J. Mayo has pointed out, is generally situated on a downward prolongation of a line following the upper part of the lesser curvature.

As Balfour points out in his remarkable report of 1000 patients observed for ten years after the making of this type of gastroenterostomy, the mortality has been low, the complications few, and satisfactory relief from the symptoms

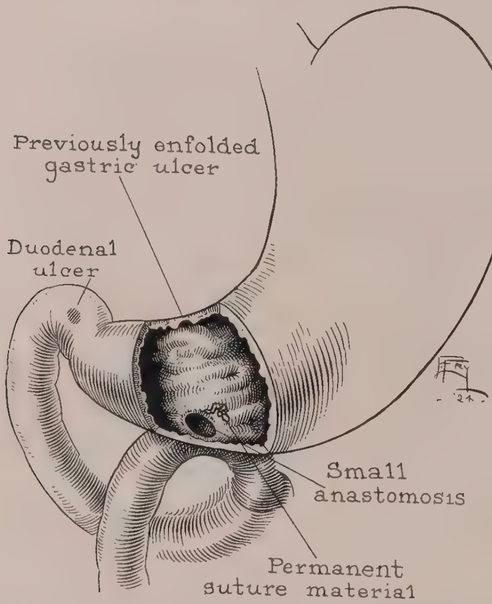

Fig. 48. Shows a gastroenterostomy with the loop running "isoperistaltically," in the patient's right.

secured in 88 per cent of the cases. He points out that the first and most important rule for the avoidance of failure is to be certain that the operation is needed. If it is not needed, that is, if there is no ulceration or obstruction at the pylorus, a gastroenterostomy is likely to make the patient worse. The second rule is that the operation be performed properly: the opening must be large, the proximal loop must not be too short, and a segment of stomach surrounding the anastomosis

should bulge, funnel-like, for a distance of at least 2 or 3 cm. below the opening in the mesocolon.

Carman (1920, p. 400) has listed the conditions that can give rise to trouble after a gastroenterostomy, and has reviewed the roentgenologic findings in 30 cases of regurgitant vomiting seen by him.

The anterior type of gastroenterostomy was formerly greatly feared but surgeons today seem to have little difficulty

FIG. 49. Roentgenogram showing the relative positions of stomach and first loop of jejunum, as located by a tube impregnated with oxide of zircon. In this case the ligament of Treitz is immediately posterior to the tube as it lies in the stomach. See also Figure 66. (*From Van der Reis and Schembra.*)

with it, and they use it without hesitation whenever, on account of peritonitis or previous operations, the posterior wall of the stomach is not available.

For a while it was fashionable to close off the pylorus in addition to making the gastroenterostomy, but the results did not prove to be any more satisfactory and the practice was soon given up. Incidentally, it should be noted that unless the mucous membrane at the pylorus is tied with a fascial transplant or cut across and sewed up, the opening will soon reestablish itself. This whole subject of closure of the pylorus is well reviewed in an article by von Tappeiner. As we shall see later, von Eiselsberg, Haberer and others

think now that the closure of the pylorus is just what one should wish to avoid when making a gastroenterostomy.

The Function of the Stomach after the Making of a Gastroenterostomy. When barium water is given to a patient with a gastroenterostomy, some of it usually runs through the stoma and on down the jejunum, but in a minute or two the emptying becomes more or less intermittent and much like that which takes place at the pylorus. As Cannon and Blake showed years ago (p. 708), this slowing is due to the rhythmic contractions of the jejunum which alternately let down and hold back the gastric contents. Unfortunately, in some cases this mechanism seems to fail, and the food continues to pour rapidly through the opening until the stomach is empty. The patient may then complain of a feeling of fullness and discomfort, and he may even have nausea and cramps. There will also be a tendency to the production of diarrhea, which in rare cases can become an annoying and even serious complication (Lehmann, 1923). In such cases the patient can often help himself by beginning the meal with dry or solid food which produces a better holding-back effect from the bowel.

Even when the gastroenterostomy has been done as it should be done, for definite disease near the pylorus, some of the barium meal will generally leave by the old opening. In a series of 65 cases, fluoroscoped shortly after operation, Case found barium passing through the pylorus in 52, but in 20 of these he had to press on the stomach in order to make it go. The waves on the stomach will always be found running to the pylorus and trying to push food out there just as they did before the gastroenterostomy.

If there is any change at all in gastric peristalsis after the operation, it becomes quieter, but in spite of this the emptying time is almost always shorter than in the normal stomach. According to Case (1925), the average emptying time in 60 patients with good clinical results was three hours and forty minutes. The meal consisted of 4 oz. of the usual watery suspension of barium followed by 10 oz. of a mixture of barium and buttermilk or warm malted milk. The emptying times were practically the same in two series of cases: one

examined three weeks after operation and the other three years after. Carman and Case agree that a gastroenterostomy opening seldom contracts much during the course of ten or twenty years, and if the patient is fluoroscoped after such an interval, the stomach will be seen to empty much as it usually does immediately after an operation.

The clinician will suspect that the operation was ill-advised if the history of the patient suggests that there never was an ulcer, and he will be still surer of it if the roentgenologist reports a normal duodenal cap. The experience of the roentgenologists at the Mayo Clinic has been that when a cap is once definitely deformed by ulceration, it stays that way for life, and this view is shared by the pathologists. Dr. Robertson tells me that he is coming more and more to depend on a shortening of the distance between the pylorus and the papilla of Vater as a sign that he must look for the scar of an old duodenal ulcer. Normally the average distance is 7.9 cm., but when scars are present it is only 5 or 6 cm. (Robertson and Hargis).

As Carman observes in his book, it is not always easy to say why a gastroenterostomy is not working well; sometimes the barium pours out so rapidly through both openings that all outlines are obscured and it is hard to say what is happening. If the stomach near the stoma is puckered upward a bit, if the jejunum is narrowed, and if a little fleck of barium can be seen near the line of anastomosis, a gastrojejunal ulcer is probably present.

Why Does a Gastroenterostomy Give Relief? One of the most striking things about a successful gastroenterostomy is the promptness with which it brings relief to the patient; his pain stops immediately, and yet we know that the ulcer must take at least three weeks to heal. Why should this be? Of course, when the pylorus has been closed off and the stomach has been full of fluid day and night for weeks, it is easy to see why the patient should feel like a new man; he can sleep again, he can get some good out of his food, his blood chlorids return to normal, the acidity of his stomach is lowered, and the waves of peristalsis are shallower and less forcible.

Changes in Acidity. In those cases, however, in which there has been little or no stasis to overcome and little acid to neutralize, it is harder to see why relief should have been obtained. I shall not attempt here to review the enormous literature on the acidity of the stomach after gastroenterostomy because, for the most part, the writers agree that there is a reduction. Apparently the free and total acids are reduced from a quarter to a half in about four-fifths of the patients.

That this lowering is due to a greater reflux of diluting fluids into the stomach and not to any inhibiting effect on the glands is indicated by the fact that the curve of chlorids in the gastric juice remains high after the operation (Bolton and others). The next question is: Why is there a greater reflux, and through which opening does the neutralizing fluid come? These questions will be taken up in more detail when I come to discuss the way in which the filling of the jejunum with food can reverse the gradient of forces in the duodenum and, when the pylorus is sufficiently patent, can increase the amount of intestinal juices forced back into the stomach.

The commonly accepted theory that it is the lowering of gastric acidity which brings relief after the making of a gastroenterostomy is unsatisfactory in that it does not explain many clinical observations. In the first place, many of the patients who fail to show any postoperative reduction of acidity have as marked and as prompt relief as those who have low acidities, and even those who later develop new ulcers often have six months or more of perfect health after the operation. Furthermore, we know that old chronic ulcers often continue to give pain and distress when the acidity has dropped to a point quite comparable with that seen after gastroenterostomies; so it is hard to see why after operation the lowering of the acid should be the important factor in bringing relief.

Another difficulty is that the relief comes so quickly. As was pointed out in Chapter XIV, it comes quickly also at the beginning of a course of medical treatment; and yet Palmer has shown that as an ulcer heals, or at least becomes quiescent, the sensitiveness of the gastric mucosa to acid

(introduced through the mouth) is lost gradually and not suddenly.

Still another difficulty is that if, after operation, a reduction in acidity were the essential factor in securing a good result, then the ulcers in the upper half of the stomach ought to heal as well as those in the pars pylorica and duodenum, and everyone knows that that is not the case. In fact, many surgeons today have so little faith in the ability of a gastro-enterostomy to effect healing in a gastric ulcer that, whenever possible, they do an excision of some kind. Today they may excise on account of the recognized danger from cancer, but originally they did the more extensive operation because the simpler one had shown itself so often to be ineffective.

There is much evidence, then, that an ulcer must be near the pylorus if it is to be benefited by the making of a gastro-enterostomy; and that suggests that the operation must in some way change the mechanics of that region. The objection to that as the only explanation is the fact that those patients who fail to get a definite lowering in gastric acidity after the making of the new opening seem to be more likely to return with more symptoms, but this is often due to the fact that they develop a new ulcer. Now that in these cases more and more surgeons are greatly lowering the acidity of the stomach by removing the pyloric third or half, we may soon be able to say how much the acid really has to do with the formation of ulcers. The recent work of Mann and Williamson has shown that in dogs chronic ulcers can be made at will by diverting the secretions that normally neutralize the gastric juice to lower regions of the bowel. Although this suggests strongly that the failure to get neutralization of the acid is the essential factor in ulcer formation, there are still many puzzling features about the disease as it appears in man; and some of the patients with the subtotal gastric resections and low acidities are already beginning to return with new gastric and gastrojejunal ulcers.

Changes in the Mechanics of Stomach and Duodenum. Much of the clinical evidence suggests to me that the making of a gastroenterostomy must immediately, in some way, take the strain off the muscle in the floor of the ulcer.

That such strain exists is shown by the fact that the muscle of the pars pylorica often becomes greatly thickened and hypertrophied; and that a gastroenterostomy puts an end not only to this strain but even to much of the normal activity is shown by the fact that after an operation the pyloric ring is sometimes found in an atrophic condition. Great credit should, I think, be given to Truesdale who several years ago called attention to these changes. His work should be repeated with care because if it should be found that atrophy of the sphincter is the rule after gastroenterostomies, much light would be thrown on the way in which the operation works.

Atrophy of smooth muscle points to one thing, and that is loss of function. Loss of function is due probably, first, to the fact that since most of the food leaves through the new opening, little is left to bear down on the pylorus and to be held back by it; and second, to the fact that food is poured into the bowel about 35 cm. below the sphincter. We should expect that to have an inhibiting effect upon the activities of the duodenum and pars pylorica because, as will be seen in Chapters XVII and XVIII, the presence of food in any part of the bowel tends to hold back the progress of material coming down from above.

The filling of the upper jejunum with food causes it to become more active than it should be as compared with the duodenum; its metabolic rate must be increased, and there must be more than the normal tendency to a reversal of the gradient of forces in the duodenum. Under these circumstances it would not be surprising if at times a current were to set backward from the stoma to the pylorus, and such a current might tend to relax the sphincter. I know that the sphincter relaxes when food stagnates in the duodenum, because under those conditions I have seen the cavities of the stomach and bowel become practically continuous. Certainly if the pylorus does relax, it ought to help the healing of an ulcer just as a temporary paralysis of the sphincter ani helps in the healing of a fissure.

That there is sometimes a reversal of the current in the proximal loop after gastroenterostomies in dogs was shown

years ago by Leggett and Maury when they found that a piece of meat tied to a string would go out of the stoma and back through the pylorus several times in succession. Occasionally, however, the current was in the other direction so that the meat left by the pylorus and returned through the stoma.

As A. Strauss has pointed out, there is often a direct relation between the depth and intensity of the gastric waves and the amount of resistance to be encountered at the pylorus, so that when the obstruction is removed, there should be a quieting of peristalsis, and such there generally is. That it should conduce to the healing of ulcers would seem obvious.

If the relaxation of the pyloric sphincter were the most important preliminary to the healing of the ulcer, it would seem as if the Rammstedt operation ought to be sufficient, but according to Strauss, it is not. In his experience with dogs, cutting the sphincter or doing some type of pyloroplasty is not sufficient to get the desired rapid emptying and shallow gastric peristalsis. In order to get them a large piece of pyloric muscle must be removed. Similar disappointments have been met with in patients in whom, unless a large amount of the pylorus is removed, and removed with great skill, the stomach often continues to empty poorly.

If an increased regurgitation of duodenal contents through the pylorus is the important factor in lowering gastric acidity and in securing a good functional result, then we should expect poor results in those cases in which the pylorus is practically closed by scar tissue. Actually, the reverse seems to be true and certainly the surgeon looks for his best results in those patients who have had the greatest degrees of retention. Nevertheless, Haberer maintains that the man with a gastroenterostomy and a closed pylorus is in a dangerous situation, in that he is more subject to the development of gastrojejunal ulcer, and if one develops and is removed he has little chance of escaping another unless the pylorus is opened or a partial gastrectomy is done. Haberer got this idea from the fact that in 644 patients with gastric resection he saw no gastrojejunal ulcers; in 262

with gastroenterostomy he saw 3, and in 71 with unilateral exclusion of the pylorus (von Eiselsberg) he saw 14.

At the Mayo Clinic Balfour (1926) analyzed the findings in 139 cases of gastrojejunal ulcer in which he had accurate records from the time of the first operation. In 130 cases, this operation was done for duodenal ulcer and in only 9 was it done for gastric ulcer. This shows that gastrojejunal ulcer is about twice as frequent with duodenal as with gastric ulcer, because the ratio is fifteen to one, and ordinarily at the Mayo Clinic only 7 duodenal ulcers are operated on to 1 gastric. Unfortunately, the data have not yet been analyzed with relation to the amount of pyloric obstruction present.

Somewhat against Haberer's idea is the fact that in Balfour's series only 40 per cent of the patients showed normal or increased acidity, another 40 per cent showed a marked subacidity and, still more remarkable, 20 per cent, on repeated testings, showed no free hydrochloric acid. Also against Haberer's idea is the fact that in a large proportion of cases there was no pyloric obstruction present. Very suggestive in relation to the greater incidence of gastrojejunal ulceration after operation for duodenal ulcer is the observation, kindly communicated to me by Dr. Klein, that anacidity is much more commonly seen after gastroenterostomy for gastric ulcer than after gastroenterostomy for duodenal ulcer.

One difficulty with the statistics from the earlier years is that many of the gastrojejunal ulcers were then due simply to the use of unabsorbable sutures, and the inclusion of these cases in any study makes it harder to bring out the significance of other factors. That this precaution is needed can be seen from the fact that in 11 out of 44 cases reported by Butsch, thread was found hanging in the floor of the ulcer. It is unfair also to include in a study of unsatisfactory gastroenterostomies those cases in which the recurrence of symptoms might easily have been due to such things as a handful of gallstones left behind at the time of operation. Actually, while making a review of a series of cases of peptic ulcer operated on at the Mayo Clinic, the thing that impressed me most was the frequency with which complicating factors are present; factors that should be excluded or held constant in

any statistical study designed to estimate the importance of certain features or procedures.

Kelling (1900) showed, in the course of his interesting study on the physiology of the upper digestive tract after gastroenterostomy, that if some of the gastric contents do not pass through the duodenum, the outflow of bile and pancreatic juice is likely to be insufficient for purposes of neutralization because the stimulus for such flow, when derived from the mucosa of the jejunum, is weak. Very suggestive is his finding that when, in dogs, the gastric contents were not sufficiently neutralized, the mucous membrane of the jejunum tended to become irritated and inflamed. (See also Mann and Williamson, and Lehmann, 1923).

In the early years, when gastroenterostomies often gave trouble, it was thought that the vomiting and other disturbances might be due to the presence of large amounts of bile in the stomach, but that idea was given up when Kelling, Chlumskij, Rosenberg, Ledderhose, Moynihan, Kölbing, Wiedemann and others showed that animals and men could live in comfort with all the secretions of the duodenum passing through the stomach on their way to the jejunum.

SUMMARY

It appears then that although none of the explanations for the relief which comes after the making of a gastroenterostomy accounts for all the facts, we can be fairly sure that the disappearance of symptoms is associated with a lessening of the strain on the pylorus and a lowering of gastric acidity which, in its turn, is due to a greater neutralization of the gastric contents. The factor that brings these changes about is probably the introduction of undigested food into the upper jejunum which irritates that region, reverses the gradient of activity in the duodenum, and thereby increases the amount of regurgitation into the stomach.

CHAPTER XVII

THE PYLORUS AND THE DUODENAL CAP

So far as one can see with the naked eye, the waves coursing over the stomach stop either at the pylorus or, as has been pointed out in the preceding chapter, a few centimeters above it. Why do they not go on down the bowel, and why are they blocked at this point? At first glance, two reasons present themselves.

In the first place, the block may be due to the anatomic peculiarities of this region (Cunningham, Aufschnaiter, Toldt, Todd, Brinton, p. 268), and in the second, to the physiological differences which, as will be shown later, exist between the muscle in the pyloric antrum and that in the duodenum.

THE FIBROUS TISSUE BARRIER. According to Cunningham and Aufschnaiter, the circular muscle of the stomach thickens at the pylorus to form a swelling in which the little bundles of fibers are more or less braided. This swelling is divided into a number of sections by connective-tissue partitions running from the peritoneum to the mucous membrane, and one of these partitions is so complete that there is little muscular connection left between the stomach and the duodenum. Most of the fibers in the outer longitudinal layer of the stomach dip down into the pyloric swelling, and only a few run over on to the duodenum. Toldt believes that these partitions of connective tissue and longitudinal muscle are remnants left behind during embryonic life, when the pyloric swelling is formed by an infolding of the wall of the primitive gut. A few of the circular fibers from the pyloric ring run down over the duodenal cap in a festoon-like arrangement, some of them becoming almost longitudinal in direction.

At the Mayo Clinic, Horton has for some time been engaged in making serial sections of the pyloric ring in many subjects and estimating the number of circular and longitudinal muscle fibers that cross from the stomach to the duodenum. His studies (to be published later as a thesis in

fulfilment of the requirements for a master's degree) show that there are narrow bridges here and there along the circumference of the sphincter, but in most places the thick layer of submucous fibrous tissue in the antrum runs outward and joins the subperitoneal layer in such a way as to divide the muscular sheets of the stomach and duodenum quite sharply one from the other. Even in those sectors in which some of the longitudinal muscle runs over across the pyloric line, it is often more or less broken up into little

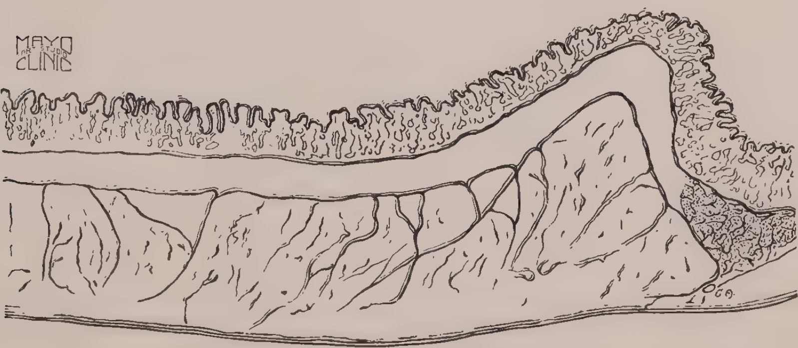

FIG. 50. Drawing of a model of a small section of the pyloric ring of an infant. Nine serial sections were drawn on glass and superimposed. Note from above downward, mucosa, submucosa, muscle with partitions of connective tissue, and serosa. The dark area in the submucosa of the duodenum represents Brunner's glands. Note the almost complete separation between the muscle of stomach and duodenum, brought about by the presence of connective tissue partitions and large blood vessels. (*From Horton.*)

bundles or whorls, surrounded by connective tissue; and in other places, the continuity of some of the muscular bridges is interrupted by the presence of large blood vessels. Horton's main contribution to the subject so far is his proof that the muscular connection between the stomach and bowel consists of narrow bridges here and there on the circumference of the sphincter, bridges somewhat like those which Kent demonstrated years ago between the auricles and the ventricles. He has shown also that Auerbach's plexus crosses over from stomach to bowel without much break; in fact

there sometimes is a duplication of the layer of nervous tissue at the pylorus.

A Physiologic Barrier. The fibrous barriers account probably for most of the blockage of the waves at the pylorus, but some of it may be due to differences in the physiologic properties of the muscles on the two sides of the pyloric line. Lillie (1920, p. 177, and 1914, p. 439) and others have pointed out that a stimulus suited to the metabolism of a sluggish muscle will often have no effect on an active one, and it may be that waves coming every twenty seconds cannot spread well into a tissue which contracts rhythmically with a period of three seconds. The difficulty with that argument, however, is that we know now that the upper duodenum contracts at times with a tonus rhythm similar to that of the stomach.

If all the gastric waves turned into systoles of the pars pylorica, we should have still another explanation for the separation between the activities of stomach and bowel, but as many of them travel peristaltically up to the pyloric line and do not run over, we must conclude that the main barrier to further progress is the anatomic one. As will be seen later, a somewhat similar barrier exists at the ileocecal sphincter.

THE DUODENAL CAP

That part of the duodenum just distal to the pylorus is not only one of the most interesting sections of the digestive tract, but it is probably the most important in the eyes of the gastroenterologist. Anatomically it is peculiar in that some of its muscle fibers are arranged in festoons (Aufschnaiter and Verson). The muscular coat is rather thin and it is fastened firmly to the underlying mucous membrane. This may be due at least partly to the fact that the glands of Brunner dip down into the submucosa. The inner surface of the mucous membrane is smooth, and shows none of the transverse folds which are so characteristic of the bowel lower down. When in roentgenograms, folds can be seen they are directed longitudinally, as in the stomach. In many ways, therefore, both anatomically and physiologically, this

short segment seems to be more a part of the stomach than of the bowel.

When the muscle from this region is excised and put into warm Locke's solution, it is found to be weak; its rhythmicity is lower than that of the rest of the duodenum, and it is highly sensitive to trauma. It is probably this weakness of the muscle that causes the cap to remain filled while the stronger regions on both sides are actively emptying themselves. The finer arterial supply is peculiar (Mall, 1896[a],

FIG. 51. Roentgenogram showing normal stomach and cap.

Wilkie, Reeves), and the nerves (vagus) come from branches supplying the liver.

This region is particularly interesting to the clinician because it is the commonest site for peptic ulcer, and also for the ulcers due to severe burns. The existence of these toxic ulcers suggests that the mucous membrane of the duodenum shares in the excretory function which is possessed by the liver and the gallbladder. As will be shown later, the gallbladder is often severely injured by the bacteria and toxins that it excretes, and it may be sometimes that a similar process takes place in the closely related duodenum. The

statistics of Robertson and Hargis have brought out the interesting fact that at the necropsy table, duodenal ulcers are found quite frequently in association with appendicitis, tumors of the brain and cord, cholecystitis, hypertrophy of the prostate, nephritis, and toxic forms of goiter.

The first portion of the duodenum may suffer also because it serves as a sort of hook from which the distal end of the stomach hangs like a hammock. As there are a

Fig. 52. Lewis Gregory Cole.

number of cases on record in which the duodenum has actually been torn in two by strong sudden contractions of the abdominal muscles, it seems reasonable to suppose that not infrequently it suffers from milder degrees of trauma.

Is the Cap Filled with Each Gastric Wave? From animal experiments we can be fairly sure that, especially at the beginning of digestion, not every gastric wave pushes material into the duodenum. As Cannon (1911[a], p. 101) says, "When protein, for example, is fed, peristaltic constrictions may press the food against the pylorus repeatedly for

a half hour or more (approximately 150 waves) without forcing food through the orifice." The experiments on dogs with duodenal fistulas indicate, however, that with water in the stomach, or with food that is already partly liquified, for considerable periods of time there come through the pylorus from three to five spurts every minute, corresponding probably to gastric waves arriving at the sphincter.

According to one group of workers (Hurst and Briggs, L. G. Cole, McClure, Reynolds and Schwartz, Wheelon and Thomas, and Klein), the sphincter in man relaxes as each gastric wave approaches the pylorus. They have been impressed by the fact that in many roentgenograms one can see a band of barium joining the shadow of the pyloric end of the stomach with that of the duodenal cap; and because this connecting shadow is so wide and so well marked in many of the roentgenograms taken at different stages of gastric peristalsis, they feel that the sphincter must be open a good part of the time. Case (1916) doubts this, however, and says, "Even when the pylorus is closed, this narrow channel, measuring about 1/8 in. in diameter, is visible owing to the adhesions of minute quantities of barium to its mucosa. This adhesion of opaque salt to the mucous lining of the pylorus has led some into the error of contending that the pylorus is always open. When the pylorus is really open the canal is seen to be widely distended, measuring as much as 1/2 in. in diameter." Kaestle studied the problem with the help of serial roentgenograms and came to the same conclusion as that reached by Cannon, that the pylorus often remains closed during several gastric cycles. Groedel also showed in man that not every wave pushes material out of the pylorus.

I cannot imagine many roentgenologists accepting the dictum that the pylorus relaxes with the approach of every wave because their *bête noire* is the man with the powerfully contracted pylorus which will not permit the cap to fill even when strong manual pressure is brought to bear on the full stomach. It may well be, however, that such spasmodic closures are due purely to nervousness, and that under more normal conditions the sphincter would relax with the

approach of each wave. If that be true, we must assume the existence of a sphincter at the distal end of the cap, for no one would claim that food goes on into the second portion of the duodenum with every gastric wave.

The roentgenogram does give the impression that there is some sort of sphincter at the tip of the cap, but so far as I know, no such structure has ever been demonstrated histologically, and Dr. Horton tells me that he is quite sure that there is no thickening of the fibers there. It may be of interest to note that Kelling (1900, p. 24) came to the conclusion that in the dog there is a second sphincter 1 or 2 cm. from the pylorus; he could feel it when he put his finger through the pylorus of the living animal.

The Emptying of the Cap. It is an interesting point that the peristaltic rushes that sweep down the bowel begin, not at the pylorus, but generally in a contraction which appears about the middle of the cap. It should be noted also that both in animals and man, these waves depart about the time that a gastric contraction approaches the pylorus. Sometimes, when the stomach is emptying rapidly, the rush wave that goes down the jejunum will have two crests, one arising in the usual contraction about the middle of the cap and the other in the contraction of the whole cap which comes when food is pushed rapidly and directly into the second portion of the duodenum. In some cases it looks almost as if the wave in the stomach had jumped the pylorus and had gone on down the duodenum with the food.

Kaestle has made careful studies of the cap, as shown in serial plates, and has described two or three different ways in which it empties itself. The whole cap may contract more or less as a unit; or after the usual contraction in the middle, the distal portion may empty systolically or peristaltically. A good discussion of the anatomy, physiology, and pathology of the cap can be found in the encyclopedic article by Berg (1926). See also Case (1916).

INFLUENCES CROSSING THE PYLORIC LINE

The studies of Joseph and Meltzer, Wheelon and Thomas, Alvarez and Mahoney, Payne and Poulton, and Ivy and

Vloedman have shown that the waves in the pars pylorica are often associated with tonus waves in the duodenum. At times some part of the gastric wave or some form of influence spreads across the barrier; and then again, conduction will fail, and powerful contractions in the stomach will have no effect on the tone of the duodenum.

In the heart, an area that develops a rate of rhythmic contraction higher than that of the sinus is said to capture the rhythm because it takes the lead and becomes the pacemaker for the whole organ; similarly, my impression is that the stomach sometimes captures an independent local tonus rhythm in the duodenum. That may not be the only explanation, but from the facts observed I think it is the most probable one. In the first place, Miss Mahoney and I (1923) noticed that sometimes when the stomach was perfectly quiet the duodenal tonus waves would run on unchanged; then we found by careful count, that groups of waves in the stomach and bowel, which at first glance had seemed to have the same rate, really had slightly different rates; and later we showed that the duodenum, and for that matter, the whole small bowel has a tonus rhythm of its own which persists even when segments are excised from the body and put into warm Locke's solution. As the rate of these tonus contractions is about three a minute, it is easy to see how at times the stomach might set the pace for them.

Now just as there are some influences crossing the pyloric line in a downward direction, so there seem to be some running backward from the duodenum onto the stomach. I can detect their influence on some of the first pyloric records made by Wheelon and Thomas, and they appeared in some of my tracings made about that time. In a recent article (Alvarez, 1927), will be found graphic records of reverse waves in the pars pylorica, originating in similar waves in the first segment of the duodenum; they were obtained from rabbits in which there was back pressure in the upper bowel produced by inflammatory areas in the ileum. We are now finding such wavelets, with a rate similar to that of the rhythmic contraction of the duodenum, recorded in some of the motion pictures of the dog's stomach; there they are

FIG. 53.

superimposed on the systolic contractions of the tip of the antrum. It was probably this type of contraction that was seen once by Hedblom and Cannon in the antrum of a cat studied with the roentgenoscope. After they put some acid into the stomach they saw 18 waves a minute.

I am inclined to think that these findings will, in later years, when we have come to understand them better, be found to have considerable clinical interest. Thus it may be that the blocks at the pylorus and ileocecal sphincter protect us from developing diarrhea; and some of those persons who from childhood are subject to looseness of the bowels may have unusually wide and numerous bridges of muscle spanning the barriers of connective tissue.

THE NEED FOR A PYLORUS

Having discussed the passage of the waves over the muscular wall at the pylorus, I must now take up the progress of material through the sphincter. A pylorus is necessary in order to save the bowel from being overwhelmed by large amounts of unprepared food. In the opinion of the older physiologists, this "keeper of the gate" had a remarkable degree of intelligence which enabled it to recognize when digestion was complete; then and only then would it relax its vigilance and allow all of the chyme to run into the bowel (Rossbach, 1890[a]). Today, of course, we know that emptying of the stomach begins as soon as food is taken, and continues intermittently until all has moved on into the bowel.

The pylorus does seem to have some discrimination, however, particularly in regard to the size of the particles in the food. It has been shown that finely divided food leaves faster than food that is coarse and lumpy (Cannon), and according to some observers, in the antrum of dogs, coarse

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Fig. 53. Records obtained by fastening threads to the peritoneal surface of the pyloric antrum, the first portion of the duodenum, and the duodenum 20 cm. below the pylorus. The animal was a rabbit, under urethane, and with the abdomen opened under Locke's solution. Note the large tone changes in the duodenum when gastric waves approached the pylorus. At x, the drop in tone shows that a rush wave had just passed on its way down the bowel.

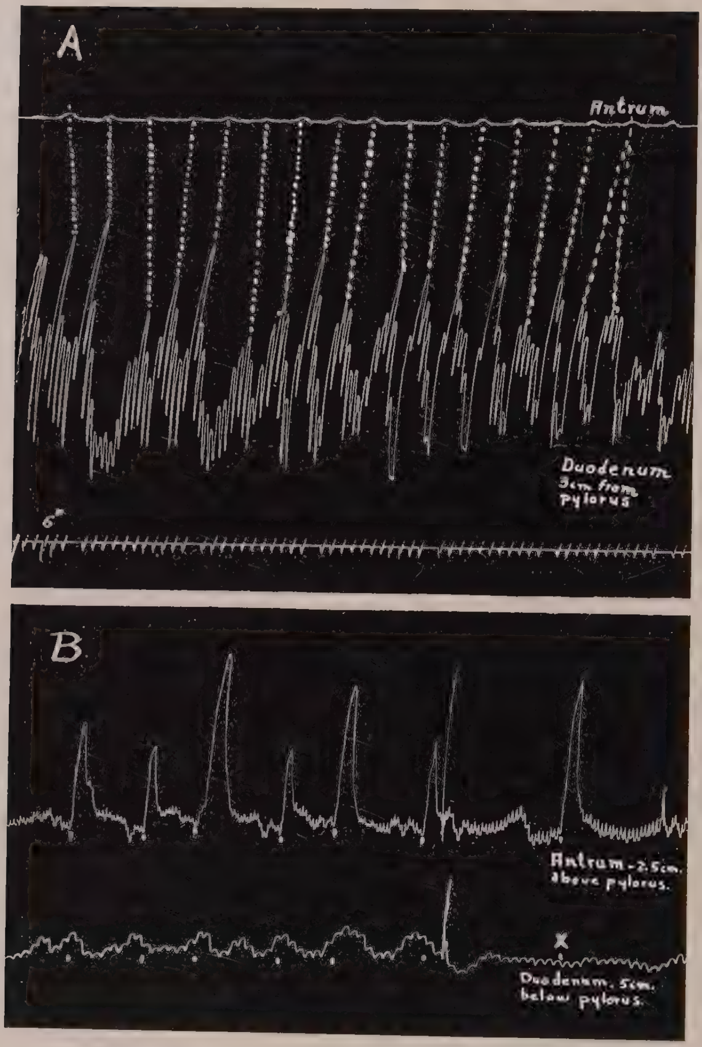

FIG. 54. A. Records from the antrum pylori and the duodenum of a rabbit. The dotted lines show that there is no relation between the gastric waves and the tonus changes in the duodenum.

B. Similar tracings showing again that the tonus rhythm in the duodenum is sometimes independent of that in the stomach. Note the failure of conduction at x.

particles such as bits of bone are at times pushed back by reverse peristalsis (Klein). Cannon (1911[a], p. 69) observed the pylorus letting through liquids and at the same time holding back solids, but he did not see reverse peristalsis connected with the process, and it certainly is not seen in normal men and women. It may be that, to a large extent, the pyloric channel with its rather narrow diameter acts simply like one of the holes in a sieve.

Cannon watched the progress of some hard pellets of bismuth in the lower end of the stomach and noted that the advancing waves pushed them forward a bit, caught up with them, and then squirted them backward through the advancing ring. In this way they gradually approached the pylorus.

Anyone who has ever passed a duodenal tube with its metal tip, or has, with the roentgen ray, watched the progress of a coin or a safety pin through the digestive tract of a baby, knows that large particles will go through the sphincter; but it takes time, and it is more likely to happen toward the close of digestion when the pylorus becomes more relaxed. According to Baird, Campbell, and Hern, the passage of the duodenal tube is very easy in patients with achlorhydria, and the relaxed state of the pylorus in that condition can easily be shown also with the roentgen ray. Some references to the older literature on the passage of large foreign bodies through the pylorus is given by Mall (1896[a], p. 109); such things have been passed as a clay pipe with a stem 10 cm. long, a table fork, and perhaps most remarkable of all, an egg cup (Dendy).

The Autonomy of the Pylorus. It was shown by Kirschner and Mangold that in dogs the pylorus will continue to function after the lower third of the stomach has been isolated, as in the Devine operation. Cannon removed the stomach and intestine from the body and found that the pylorus worked very much as it did in the intact animal; and a number of observers (Cannon 1906[a], Carlson, Thomas and Wheelon, and Borchers, 1921) have seen little or no difference in its behavior after section of all the extrinsic nerves. It would seem, therefore, that the mechanism that controls the pylorus must be resident in the tract itself.

THE CONTROL OF THE PYLORUS

Early Theories. Strange to say, after fifty years of experiment and debate, we are still uncertain about the factors that control the emptying of the stomach. Most recent authorities give Hirsch the credit for being the first (1893[a]) to note that neutral or alkaline fluids leave the stomach more rapidly than acid ones, and to point out that this is due probably to the absence of the normal acid-closing effect from the duodenal side of the pylorus. Hirsch does indeed deserve great credit for his excellent work, but as he points out, von Pfungen and Ullman in 1887 had already noticed in their patient with a gastric fistula, that alkalies and acids affect the tone of the pylorus; and the possibility that a certain degree of acidity in the stomach is necessary for the passage of the chyme into the duodenum was then being generally discussed.

We can find the idea well expressed by Ewald and Boas in their remarkable paper written in 1886 (p. 292). Their experiments suggested the presence of an acid control, but they hesitated to accept it as a rule because it did not seem to fit in well with the fact that the stomachs of patients with hyperacidity often empty slowly. To show how up to date they were, I need only point out that they used the fractional method of gastric analysis, and dyes for indicators, and made curves showing the rise and fall of free acid. It is strange that the use of this method should have been for a time somewhat forgotten because it is mentioned in so accessible a place as Ewald's lectures on digestion, translated into English and republished by the New Sydenham Society in 1891. What popularized it was the introduction of the narrower and softer and much more convenient Einhorn and Rehfuss tubes. Incidentally, Ewald says (1891, p. 124), "Most authors incline to the view that the emptying of the stomach contents through the pylorus into the duodenum depends, normally, upon the degree of acidity present."

Another interesting old article is by Oppenheimer who wrote in 1889. He apparently was well acquainted with the early studies on the acid control of the pylorus but felt that

there were serious objections to be met. Knowing nothing about the frequency with which ulcers occur near the pylorus, he fell easily into the error, common in that day, of ascribing to gastric hyperacidity the delays in emptying which we now know are due to ulceration and contraction of the outlet. That he knew a good deal about the control of the pylorus is shown, however, by his wise remark that its opening is probably not so much a function of the stomach as of the bowel.

FIG. 55. C. A. Ewald.

Another man who was well ahead of his time was Schüle (1895–1896). Using modern methods of fractional analysis, he studied the ways in which different foods bind the acid in the stomach and noted that an excess appeared usually about the time that the sphincter relaxed. He naturally was inclined to accept the view that the acid was responsible for the opening of the pylorus but he did not see how that could be reconciled with the rapid emptying seen with achlorhydria, and the slow emptying seen with hyperacidity.

THE MERE PRESENCE OF LIQUID OR FOOD IN THE DUODENUM. During the next few years many workers showed

that the presence in the duodenum of almost any liquid or food will hold back the progress of material through the pylorus. It is a striking fact, commented on by Hirsch (1893[b]), v. Mering (1893), Marbaix, Kelling (1900), Tobler, Otto, Cohnheim (1907), London, Bickel, Baumstark and Cohnheim, and others, that if the material that comes through the pylorus is allowed to run out through a fistula in the upper duodenum, the stomach will empty very rapidly, but if the fistula is closed, or if the material coming out of it is gathered and injected back into the bowel below the opening, the stomach will empty normally. As Hirsch showed, the rapid emptying is the more striking the nearer the fistula is made to the pylorus, and when it is only 4 cm. below, strongly acidified solutions will run out like water. Nearly all the workers agree that when such a fistula is open, 400 c.c. of water will run out of the stomach within twenty-five minutes, and when it is closed, the process will take over an hour.

This restraining effect from the bowel does not seem to be due so much to an irritation of the mucosa as to an increase in the activity of the muscle. This is shown by the fact that it can be brought out by putting through the fistula such non-irritating substances as physiologic salt solution (Hirsch, 1893[b]) or milk (v. Mering, 1897, Marbaix, Kelling, 1900, p. 310, and Brunemeier and Carlson). It seems, therefore, that just as activity anywhere in the bowel tends to hold back the progress of material in loops orad to it, so it can hold back the progress of material in the stomach; and just as an increase in tone and activity in a loop of bowel tends to speed the progress of material in loops caudad, so an increase in the tone and activity of the stomach can cause it to empty faster. As will be shown later, there is a balance between the downward-driving tendency of the stomach and the holding-back tendency of a full and digesting small intestine: a balance that can be upset in many ways. An ingenious way of upsetting it was devised by Kreidl and Müller who produced gastric stasis in dogs by removing the muscle from the wall of the stomach.

Mechanical Factors. These mechanical factors are perhaps the most important ones in controlling the passage

of material through the pylorus, and as such, they must be watched for, and, so far as possible, kept constant in any studies made on the chemical side of the problem. That in the past such precautions have always been taken is more than doubtful, and much of the work that has been done on this question of pyloric control is of uncertain value because the workers did not publish all the details of their technic, and we cannot be sure that the factors of intestinal and gastric filling, of appetite, thirst, disgust, excitement, fear, and worry did not enter in.

A large meal that distends the stomach will generally leave faster than a small one, and a second one will hurry the emptying of the first (Lüdin, Moritz, Katsch, 1912, Cohnheim and Dreyfus, 1908, and others). Marbaix found that 250 c.c. of water left his stomach much faster if he put 250 c.c. of air on top of it. Cohnheim and Dreyfus, 1908[b], p. 58) found in a dog that when little food was in the stomach, 10 c.c. of gastric contents injected through a fistula into the duodenum closed the pylorus for from ten to fifteen minutes, but when the stomach was full, the same stimulus stopped the flow for from one to one and one-half minutes.

Food eaten with pleasure will leave the stomach faster than when it is put in with a stomach tube (Haudek and Stigler, p. 159, Hurst, 1912, Gilmer, Takahashi, and Sailer), apparently because with appetite there is a psychic increase in the tone of the gastric muscle. On the other hand, as will be shown later, disgust, worry, and fear will either weaken peristalsis or in some way block for hours the emptying of the stomach. According to Best and Cohnheim (1910[a,c]) the thirst of an animal has much to do with the rate at which fluids leave the stomach, and sham drinking will greatly speed up the process. See also Wheelon and Thomas (1922).

The distention of the duodenum by a balloon (Tobler and Carnot, 1907) or by food, or the irritation of the bowel by strong saline solutions, or by tickling with a feather (Katsch, 1912), will retard the emptying of the stomach. Cohnheim and Dreyfus (1908[b], p. 58) put 4 per cent solutions of sodium chlorid and magnesium sulfate through

a fistula into the upper bowel and produced marked slowing of gastric emptying, with nausea and even vomiting, and Baumstark produced a similar slowing when he put fermented food through fistulas into different parts of the small intestine. Kelling (1900) showed that this slowing is much more marked with food in the duodenum than with food in the jejunum. It is doubtless this holding-back effect of intestinal peristalsis which keeps the food from pouring out of the stomach after gastroenterostomy and pyloroplasty.

This was shown beautifully by Kelling (1900) who reversed the direction of loops of jejunum so that peristalsis would run orad, and then used them for the distal limb of a gastroenterostomy. Even when the loops were only 25 cm. in length, they produced so much back pressure that the emptying of the stomach was greatly delayed, and one dog vomited almost continuously.

To sum up, then, I think it obvious that we must be careful how we speak of the retarding action on the duodenal side as an "acid" reflex. The acid is effective, but so also, as we shall see, is fat.

Influence of Fat. It was discovered by the early workers that fats and their split-products, when placed in the duodenum, can markedly slow the emptying of the stomach (Ewald and Boas). According to Lintvareff (1903) and Babkin (p. 383) who made a particular study of the problem, the latent period for the closing reflex is the same with fat as with acid, but the effect of the fat lasts longer. The "fat" reflex can be obtained from almost any part of the small bowel, but it becomes weaker the nearer the stimulus approaches the ileocecal sphincter, and according to Best (1911) it disappears at a point above that where the acid reflex does. It is not elicited by vaselin (Babkin, 1914, p. 383).

As with acid, so with fat, much depends on the way in which the pancreatic juice and bile are poured out. According to Jarotzky (1927), if one puts 100 c.c. of sunflower oil through a tube into the duodenum of a man, and then, with another tube, determines the rate at which a measured amount of water leaves the stomach, one can get an idea of the functional activity of the pancreas and the gallbladder.

FURTHER STUDIES ON THE ACID CONTROL. As has been shown, the early workers in the eighties seriously considered the idea that free acid in the stomach opens the pylorus, but were rather discouraged by the failure of the theory to fit in with clinical observations. In the next twenty years more attention was paid to the closing effect of acid on the pyloric side, until it was pretty thoroughly demonstrated, at least for 0.5 per cent hydrochloric acid.

Babkin thinks that much credit should be given to Serdjukoff (Babkin, p. 377) who, in 1899, showed the importance for pyloric closure of the neutralization of the gastric contents by the pancreatic juice. What happens when this juice is excluded from the duodenum can be seen from the following table which shows the rates of gastric emptying with acid and alkaline solutions in a dog with a permanent pancreatic fistula.

Amount put into the stomach	Amount still in the stomach after fifteen minutes
200 c.c. 0.5 per cent HCl	185 c.c.
200 c.c. distilled water	37 c.c.
200 c.c. 0.5 per cent Na_2CO_3	18 c.c.

It seems clear from this that if the acid is left unneutralized in the duodenum, it will keep the pylorus closed for long periods of time.

Since Serdjukoff's day, a great deal of work has been done by many experimenters, most of whom agree that concentrations of hydrochloric acid between 0.2 and 0.5 per cent, in the duodenum, will slow the emptying of the stomach. A number of them (Best, 1911, and Barsony and Egan) have found that weaker concentrations have little or no effect, and this is important because several workers (Best and Cohnheim, 1910[a,b], Luckhardt, Phillips and Carlson, and Baird, Campbell, and Hern) have noted that the material coming through the pylorus often contains no free acid and rarely much "total" unless large amounts of acid water have been put into the stomach. One wonders, therefore, whether there is normally enough acid in the chyme to

close the pylorus, and whether the usual temporary inhibitions of emptying may not be due simply to the presence of products of digestion in the duodenum.

Incidentally, it may be of interest to note that Marbaix and Best (1911) found that acid placed even in the middle or lower third of the small bowel will slow the emptying of the stomach. Strong concentrations of acid, up to 1 per cent, placed in the duodenum generally produce vomiting (see also Ivy and McIlvain), and when present in the stomach they give rise to the secretion of large amounts of diluting fluid. Cohnheim and Best (1910) showed that a preliminary injection of novocain into the duodenum will prevent the acid from slowing the emptying of the stomach. Barsony and Egan found that the acid reflex is not so easily demonstrable in anesthetized dogs, so anesthesia had better be avoided in further work along this line. Several workers (Marbaix, von Mering, 1897, Cohnheim and Best, 1910, Dagaew and Cannon) have found that the acid reflex persists after the pylorus has been wholly or partly excised, or the duodenum cut in two (von Mering, 1897); but the effects are not so marked.

Hirsch made a particular study of the restraining effects of acids other than hydrochloric. He found that 0.5 or 0.7 per cent acetic acid ran out of the duodenal fistula much like water, but in concentrations of 1.2 per cent it was vomited. Lactic, citric, and butyric acids, with a concentration about N/10, went out rapidly, but sulphuric, phosphoric and tartaric acids went out slowly. (See also Carnot and Chassevant, 1905[c]). The fact, noted by Morse (1918) that tabasco sauce in water did not tend to slow the emptying of the stomach, suggests that an inhibiting effect is not produced simply because a substance is irritating to the mucous membrane of the duodenum. It may be, however, that pepper is irritating only to taste-buds in the mouth and not to digestive mucous membranes in general. That chemical substances other than acids and fats can have an inhibiting effect was shown by Moritz (1895[a]) who found that beer and bouillon leave the stomach much more slowly than water, and by Carnot and Chassevant (1905[a,b]) who found that hypo- or

hypertonic solutions of sodium chlorid or glucose also go out slowly.

Many workers have puzzled over the problem as to the way in which the inhibitory stimulus from the duodenum acts; that is, does it weaken the contractions of the stomach or does it close the sphincter, or does it do both? Cannon concluded from the fact that deep waves continue to course over the stomach when food has passed into the duodenum and jejunum, that the main effect must be on the sphincter. Schoemaker and others have pointed out, however, that in addition, there is probably some weakening effect on peri-

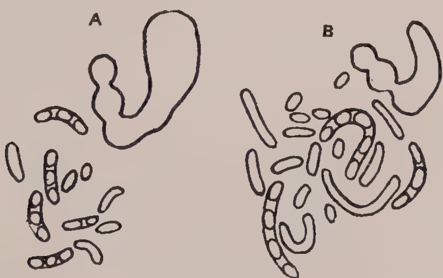

FIG. 56. Tracings of the shadows on the fluorescent screen of the contents of the stomach and bowel in a cat two hours after feeding, in one case, (A), boiled lean beef, and in the other, (B), boiled rice. The small divisions in some of the loops represent rhythmic segmentation. (*From Cannon.*)

stalsis, because after the pyloric region has been resected, the placing of acid in the duodenum still tends to retard the emptying of the stomach.

Barsony and Egan claim also that 15 c.c. of 0.36 per cent HCl put into the duodenum of a man will depress the tone of the stomach and stop peristalsis, but such large amounts are not normal as was shown by the fact that they produced dizziness and nausea. A similarly produced inhibition of the antral movements was noticed also by Kirschner and Mangold in the dog. Carlson and Litt put a balloon into the pylorus and found that any stimulus, acid or alkaline, in the duodenum would cause contraction of the sphincter. Stimulation from the gastric side had no effect. Brunemeier and Carlson found also that any stimulus from the duodenal

mucosa would depress the tone of the fasting stomach and stop hunger contractions.

Cannon's Contribution. As I have pointed out, when Cannon, in 1904, published his first paper on the control of the pylorus, the idea of an acid reflex had been under discussion for a good many years. Little doubt remained about the ability of hydrochloric acid to close the pyloric door behind it, but it was very questionable if it could open the door ahead of it. There was some evidence in favor of this view because Hirsch, Penzoldt, and Schüle had shown a relation between the rate of emptying and the appearance of free acid in the stomach, but as the early writers pointed out, this evidence might or might not mean that the opening of the pylorus was due to the acid. Furthermore, some experiments had suggested that alkalies open the pylorus and acids close it.

Cannon's name will always be connected with this subject because while his predecessors had spoken hesitatingly on the basis of comparatively few experiments, he came out definitely with much convincing proof that acid in the stomach does open the door ahead of it. As a result, the theory was immediately well received; it was simple and apparently well suited to the needs of the situation, and, in addition, it seemed to fit in perfectly with the already accepted law of the intestine.

Unfortunately, the writers of textbooks, with their liking for positive and unqualified statements, failed to note that Cannon as well as his predecessors had seen defects in the theory and some places in which it would not work. He saw that it did not explain the behavior of liquids, which run through the stomach without waiting to be acidified; he saw that it did not account for the rapid passage of white of egg, and it did not account for the extremely slow emptying of the fats. It failed also in the clinic where it did not account for the rapid gastric emptying seen in cases of achlorhydria, the slow emptying seen in many cases of gastric ulcer, and the initial rapid emptying in cases of duodenal ulcer. Neither did it fit in well with the fact that the stomach continues to empty intermittently and fairly normally after

pylorectomies and gastroenterostomies (Cannon and Blake, v. Redwitz, Judd, Finney and Friedenwald, Marbaix, p. 283, and v. Gehuchten, p. 277) because one would not expect an intricate mechanism to work well after the removal of its most essential part.

Unfortunately, also, almost all of those who have since attempted to demonstrate the acid control of the pylorus have failed, and as a result, no one knows now exactly what to think about the subject. It will probably be helpful first to see what evidence Cannon had gathered when he proposed

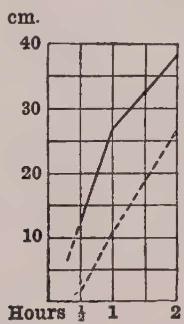

FIG. 57. These and other similar curves from Cannon's book show the average aggregate length of the food masses in the small intestines at hourly intervals after feeding.

The continuous line represents the average rate of passage into the bowel of potato, rice and crackers (four cases each), moistened with water, and the broken line the same moistened with a 1 per cent solution of sodium bicarbonate. (*From Cannon.*)

his theory; fortunately, he has summed it up for us on page 106 of his book:

"Moistening carbohydrates with $NaHCO_3$ retards their normal rapid exit from the stomach; feeding proteins as acid proteins remarkably hastens their normally slow exit; observations through a fistula in the vestibule show that an acid reaction closely precedes the initial passage of food through the pylorus, that the introduction of acid causes pyloric opening, and that delaying the acid reaction causes retention of the food in the stomach, in spite of strong peristalsis; and, when the stomach is excised and kept alive in

oxygenated Ringer's solution, the pylorus is opened by acid on the gastric side."

Now which of these observations have been repeated, which confirmed, and which questioned? So far as I know, the studies with a fistula in the vestibule have not been repeated; instead, experimenters have given alkaline and acid fluids by mouth, or have put them in through a Rehfuss tube. I doubt also if the experiment with the excised stomach has been repeated.

I think there is no doubt about the rapid emptying of carbohydrates as compared with proteins, as it seems to

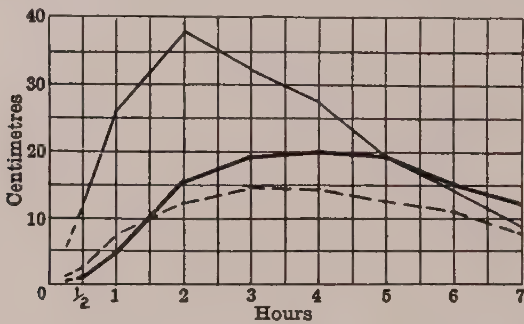

FIG. 58. The heavy line represents the rate of passage through the pylorus of protein foods, the light line, of carbohydrates, and the broken line, of fats. (Each average represents sixteen experiments.) (*From Cannon.*)

have been demonstrated by everyone who has looked for it. It was seen probably by Haller in the 18th century, and by Ewald and Boas in 1886, and it is recorded definitely by Penzoldt (1894, p. 230), Schüle, Fermi (1901[a]), Cannon (1904, 1907), Hedblom and Cannon, Best, Wulach, Jaros, Demuth and Hawk, and Rehfuss and Bergeim. In a general way it was shown by Beaumont in 1833, when he found that St. Martin could digest starches in from one to three hours and meats in from three to five hours. There were some curious exceptions to the rule, however, as with soused pig's feet and tripe which digested in an hour!

Cannon concluded that the carbohydrates leave promptly because, unable to combine with the acid, they allow it to

appear early in a free state; the proteins, on the other hand, leave late because they combine with the acid and keep it from getting free until gastric digestion has continued for an hour or two. This is one explanation and a good one, but as Schüle has pointed out, there is also the possibility that the food leaves about this time because much of it is then becoming so liquid that it can easily be squirted through the sphincter.

Consistency of the Food. The consistency of the food should, then, have much to do with the rate at which it leaves the stomach; and theoretically, if the carbohydrates were as difficult to liquefy as meats they should go out as slowly as meats. This may explain also why raw white of egg, which is semi-liquid, leaves the stomach promptly like water, and not slowly like other proteins. When it is eaten cooked, it leaves slowly (Luciani, p. 217). Actually there is a good deal of evidence in favor of the view that the main work of the stomach is accomplished when it has liquefied its contents or at least turned them into pap, and that when that is done, the material can go into the duodenum no matter what its acidity.

In accordance with this view is the fact that liquids generally run out of the stomach in a few minutes; also that when carbohydrates are fed in the form of dry hard masses they leave much more slowly than when fed as gruel (Penzoldt, Schüle, Fermi, 1901[a], and Hedblom and Cannon). Fermi showed that bread crumbs and poorly cooked rice and macaroni may be digested even more slowly than meat. His technic was good, as he allowed his dogs to eat heartily, killed them after an interval, and then found the dry weight of what was left in the stomach. His index figure for meat ranged between 9 and 12 units; for well-cooked rice it was 8, for partly cooked rice it was 14, and for rice practically uncooked it was 34. This figure should be compared with 15 for bread crumbs, 16 for oil, 18 for butter and 28 for lard. Similarly, he found with meat that the rate of emptying was fastest after it had been boiled and slowest after it had been roasted; in between were the rates for raw and broiled meat.

Similarly, Moritz (1895[a]), Cohnheim (1907), and Hedblom and Cannon found that meat leaves the stomach sooner if it is hashed before it is eaten, and starch leaves very slowly if given in the form of dry, hard balls. Best and others have suggested that the rapid emptying of starchy foods can be explained partly by the fact that they do not wait for complete liquefaction in the stomach but go out in a lumpy mushy state. Strange to say, white bread goes out more slowly than coarse. (Hedblom and Cannon, and Best.)

Hirsch (1893), Moritz (1901), and Ortner came to the conclusion that the consistency of the food and the rate at which it becomes liquefied in the stomach is the big factor in gastric emptying. As soon as there is some fluid material present it is squirted through the pylorus and the solids are left behind. Best is apparently the only one who thinks that the consistency of the food and the extent of its preparation in the kitchen are unimportant factors. His technic, however, was not so good as that of Fermi or Hedblom and Cannon.

Alkalized or Acidified Food. The attempts to show retarded emptying with alkalized carbohydrate, and more rapid emptying with acid protein have not been so successful, but before taking up the evidence adverse to Cannon, I think, in all fairness to him, it must be emphasized that no one has tried to repeat his experiments with his delicate technic. He fed cats with stiff mixtures of bismuth and food, and then, from hour to hour, measured the total length of the ovoid shadows on the roentgen-ray screen. By plotting the figures that he obtained in this way, he was able to tell more about the rate of emptying of the stomach than if, like subsequent investigators, he had simply tried to estimate the size of the waning shadow of that organ. Perhaps on account of the lack of a roentgenoscope in many physiologic laboratories, this method has since been used but little. That it is perfectly practicable was shown by Hedblom, who worked with Cannon, and by Magnus, Padtberg, and Van der Willigen, who used it for pharmacologic studies.

When we come to see later how large a part nervous influences, anxiety, fear, discomfort, pain, disgust, and excitement play in the control of the pylorus, we shall have cause to

wonder how much can be learned about the "physiology" of this sphincter with some of the methods that have been used. It is questionable also if a pylorus can act normally when it has a foreign body fixed in its lumen as in the many experiments with duodenal tubes. Another important point to be noted is that most of the workers have used either liquid or semi-liquid test meals which behave quite differently from the pastes used by Cannon and Hedblom.

THE TECHNIC OF VARIOUS WORKERS. On reviewing some of the studies of pyloric function made in the last thirty years, I find fourteen workers or sets of workers who used human subjects. Hirsch, Moritz, Meyer, Cowie and Lyon, Neilson and Lipsitz, Theile, McClure, Reynolds and Schwartz, and Spencer, Meyer, Rehfuss and Hawk used stomach tubes; Egan used the stomach tube and the barium meal; Barsony and Egan used the barium meal and stomach and duodenal tubes; Baird, Campbell, and Hern used stomach and duodenal tubes, and Bergmann, von Tabora, and Palmer used the barium meal. Fifteen workers used dogs. Hirsch, Cohnheim, Cohnheim and Best, Best, and Ortner studied the function of the pylorus through duodenal fistulas; Brunemeier and Carlson used gastric and duodenal fistulas; Cohnheim, duodenal fistulas and a tube in the stomach; Schüle, the stomach tube; Morse made an esophageal fistula, destroyed part of the dorsal cord and used a tube in the stomach; Klein's dogs were anesthetized, the vagi were cut at a previous operation, and the abdomen was opened; Kirschner and Mangold's dogs had had a Devine type of operation performed, and were probably anesthetized and with the abdomen open. Carlson and Litt used barbital or ether and put a balloon in the pyloric canal; and Luckhardt, Phillips, and Carlson, and Barsony and Egan used balloons in the stomachs of animals with various fistulas. Some of Barsony and Egan's animals were anesthetized. Cannon, Hedblom and Cannon, and Lenk and Eisler used cats which were given barium meals.

A Summary of Research Done. Although, as one would expect, some of the work is convincing and some is not, there is enough agreement on most points so that I

think we can feel fairly safe in drawing conclusions. In the first place it appears that strong acidification, with hydrochloric acid, of liquids or foods will delay their passage through the pylorus until the acid has been diluted or neutralized to a point where it will not be so stimulating on the duodenal side. We can feel the surer of this as it was observed by Hedblom and Cannon. In their experiments, lightly acidified carbohydrate food went out faster than normal, but similar food, strongly acidified, went slowly. Similar observations have been made by Baird, Campbell and Hern, who found that after the acid solution was partially neutralized in the stomach it left quite rapidly, as if the usual inhibiting mechanism on the duodenal side were not functioning.

Spencer, Meyer, Rehfuss and Hawk showed that alkalies will behave in much the same way as acids; weak solutions will hasten emptying, but strong ones will be held in the stomach until they are diluted and made less irritant for the duodenum. They confirmed the slow emptying of strong acid solutions as did also Ortner, Moritz, Carnot and Chassevant (1905[c]), Lenk and Eisler, von Tabora, and Morse. In agreement also are probably the results of Cowie and Lyon, and Neilson and Lipsitz.

Carnot and Chassevant (1905[c]) studied at the same time the effects of acidity and osmotic pressure, and found that although, ordinarily, strongly acid solutions leave the stomach very slowly, if the osmotic pressure should happen to reach a certain point, they may pour out into the duodenum quite rapidly. If this is true (and Carnot is an excellent worker), much about the control of the pylorus which is now obscure might be cleared up; and at any rate, it shows the need for watching a number of factors at the same time. Against the idea, of course, is the fact that water runs rapidly out of the stomach, probably before its osmotic pressure has been greatly altered.

Among those who could not see that acid had much if any effect one way or the other were Theile, using milk; Egan, using liquids given by stomach tube; McClure, Reynolds and Schwartz, using an excellent technic with meals of carbohydrate, meat, or fat, of constant consistency; Luck-

hardt, Phillips and Carlson, using fluids, and Klein, using meat soup. It is interesting that Hirsch, who showed definite effects with acid in dogs, could not show them in man.

Baird, Campbell and Hern, McClure, Reynolds and Schwartz, and Barsony and Egan found difficulty in showing even the acid-closing phenomenon from the duodenum, and with Luckhardt, Phillips and Carlson, they doubt the ability of the small amounts of free acid left in the chyme, when it comes through the pylorus, to exert any effect. Meyer studied the rates of emptying of two types of test-meal in men with subacid and hyperacid stomachs. One meal contained 50 gm. of bread with barium and 250 c.c. of tea, and the other 140 gm. of beef with barium and tea. After an hour he pumped out the stomachs and determined the amount of dry substance remaining. No significant difference was found in the behavior of the stomachs in the two groups.

As has been noted, strong alkalies in the stomach will delay emptying, but according to Schüle (p. 72), Theile, and von Pfungen and Ullman, moderate alkalinization will speed it. Egan (1915), McClure, Reynolds and Schwartz, and Klein could see no effect. Lenk and Eisler found emptying more rapid, but they gave two "coffee-spoonfuls" of magnesium oxide to a cat, so their experiment belongs more in the field of pharmacology than in that of physiology.

Nearly all the workers agree that fluids tend to leave the stomach immediately unless their reaction is markedly acid or alkaline, so it seems probable that if an experimenter wishes to show the favorable influence of the acidification of gastric contents on emptying he will have to follow Cannon and use a solid meal.

The idea of an acid control of the pylorus is dependent largely on the belief that the duodenal contents are normally alkaline and that this alkalinity is upset for a moment by the arrival of acid contents from the stomach. It is disturbing, therefore, to find now that the duodenum is not so alkaline as was formerly assumed. In man the hydrogen-ion concentration seems to range from pH 3.0 to pH 8.0 (McClendon and his associates, Hume, Denis, Silverman and Irwin,

1924, McClure, Wetmore and Reynolds, 1921, and Okada and Arai). In dogs the range is somewhere between pH 5.2 and pH 6.2 (Arnold). The bowel seems to be more acid in the presence of certain foods such as protein. In some animals the reaction seems to be acid all the way to the ileocecal sphincter. An entrée to the literature on the subject can be obtained through the articles already quoted, and through those of McClure, Montague and Campbell (1924[a,b]) Schiff, Eliasberg and Mosse, and Long and Fenger. According to McWhorter (1918) and Kahn and Stokes the pH of pure gastric juice ranges between 1.0 and 1.5 and that of ordinary gastric contents ranges up to 2.1. Peptic activity stops with acidities below pH_4 and dimethylamidobenzol also fails to react below this point.

McClure, Reynolds and Schwartz, using duodenal tubes and normal men, kept the first portion of the duodenum neutral for a time without upsetting the intermittent opening and closing of the pylorus, and Baird, Campbell and Hern (p. 43) kept it acid for some time without being able to stop the outflow from the stomach.

The Effect of Osmotic Pressure. There is some evidence to show that just as the stomach protects the bowel from irritation by too great a concentration of acid or alkali, so it will protect it from insult by fluids with too great an osmotic pressure. Thus Moritz (1901), Otto, Best, and Carnot and Chassevant (1905[a,b]) found that physiologic salt solution leaves the stomach a little faster than water, and Schüle, and Carnot and Chassevant (1905[b]) found that strong concentrations of glucose retard gastric emptying.

Carnot and Chassevant have shown clearly that sodium chloride and glucose can act in the duodenum much as acids do, and can keep the pylorus closed until the osmotic pressure of the gastric contents is brought nearly to that of the tissues. Isotonic solutions run out rapidly, hypotonic ones more slowly, and hypertonic ones still more slowly. There is also a specific effect from the substance used because isotonic solutions of glucose leave the stomach more slowly than isotonic solutions of sodium chloride. Apperly has also come to the conclusion that the gastric contents must be

brought nearly to the osmotic pressure of the tissue-fluids before they can leave the stomach. That they do not have to be brought exactly to normal is shown by the fact that water pours out of the stomach so rapidly. To my mind these observations are important and do not merit the oblivion into which they have fallen.

The Effect of Position. It has been shown by a number of workers that, as one might expect, the stomach empties more rapidly with the subject lying on the right side (Link, Neilson and Lipsitz, Moritz, 1901, Jolasse and many others).

The Effect of Heat and Cold. The influence of heat and cold has been studied by many workers, and they all agree that there is not much difference between the rates of egress of warm and cold fluids, but the warm probably go out a little faster (Hedblom and Cannon, Leven, Best and Cohnheim, 1910[b], and Moritz, 1901). So far, then, as animal experiments go, I can see no justification for the way in which many surgeons deprive their patients of *cold* water.

REGURGITATION OF DUODENAL CONTENTS INTO THE STOMACH

No theory in regard to the control of the pylorus can be entirely satisfactory unless it throws some light on the now well established fact that, especially toward the close of digestion, some of the contents of the duodenum run back into the stomach (Kussmaul, Boldireff, 1904[a], and 1915, Rehfuss, Bergeim and Hawk, and Ivanoff). The phenomenon is of great interest because it seems to have a good deal to do with producing the drop in gastric acidity that takes place at a certain stage of digestion, and because disturbances in this neutralizing function probably play some part in the production and maintenance of peptic ulcer.

Unfortunately, little is known about the type of muscular action that brings about this back-flow. From some studies on animals, Hicks and Visher concluded that it is due probably to the rhythmic segmenting movements of the duodenum. In man, I have often seen strong waves in the second portion of the duodenum throwing the barium mix-

ture back toward the pylorus, but they seemed to be but a part of the rhythmic to-and-fro movements.

It seems most probable that the duodenal contents flow backward during the intervals when the pressure in the pars pylorica is lower than that in the cap. As will be seen later, fluids can travel long distances in the small intestine without the help of any forwarding peristalsis, and Boldireff (1904[a]) noticed in fasting dogs with a gastric fistula that considerable amounts of intestinal juice will run out almost continuously. This regurgitation was increased when 0.1 per cent hydrochloric acid was placed in the duodenum. Best and Cohnheim (1910[c]) made the interesting observation also that sham feeding of such a dog will stop the regurgitation, probably because it raises the tone of the stomach above that of the duodenum.

It is suggestive that the regurgitation of duodenal contents is more marked when fats have been eaten because, as is well known, they lessen the tone and activity of the stomach (von Tabora, Cannon, 1907, p. 315, and Boldireff, 1904[a]) and increase that of the duodenum (Bokai 1887[b]), and that is just the type of reaction which might reverse the gradient of pressure between the two organs.

According to Bolton and Goodhart, "duodenal regurgitation is not an intermittent leak into the digesting stomach in small amounts, but at a definite point, as the stomach is emptying and the curve of activity is rising, the pylorus relaxes and allows of a considerable reflux of intestinal juices, which rapidly brings down the acidity as the stomach empties, and determines the form of the curve." This seems very doubtful because in some cases bile can be found in every sample of gastric contents removed for a fractional test.

Duodenal antiperistalsis has been seen quite commonly by Henderson in patients infested with hookworms; there it must be due to the irritation of the bowel by the parasites. Reverse peristalsis in the duodenum associated with a certain amount of stasis has been well described also by Wheelon (1920, 1921).

It is suggestive that Carnot (1913) found with the perfused small intestine that the duodenum was the one place

in which he could see reverse waves. They ran toward the pylorus and served to hold back the gastric contents. This agrees with my finding that in dogs the gradient, particularly of latent period, is almost always downward from the first part of the jejunum to the pylorus.

NERVOUS REFLEXES INVOLVING THE PYLORUS

My first observations on the physiology of the stomach date back to a day some thirty years ago when I happened to be helping my father set some broken bones for a girl who early that morning had fallen out of a fruit tree. The accident had taken place many miles out in the country, so it was after noon before her parents could get her to the city. On being given a few whiffs of ether, she vomited, and I can still remember my surprise at seeing the fruit she had eaten hours before, returning unchanged, and with the marks of her teeth clearly chiseled on the surfaces.

Years afterward I saw this same complete stoppage of digestion in a child who, immediately after breakfast, succeeded in tipping herself over backward in her high chair. She was badly frightened, but seemed all right until shortly after noon when she became acutely ill and vomited unchanged the food eaten at breakfast.

Minor degrees of this sort of thing are seen every day by the roentgenologist in those patients who are particularly apprehensive about the examination; and many of the functional disturbances of digestion are almost certainly due to these psychic inhibitions of all the functions of the stomach. Some ancient sage was a good physiologist when he said, "Better is a dinner of herbs where love is, than a stalled ox and hatred therewith" (Prov. 15: 17) and "Better is a dry morsel and quietness therewith than a house full of feasting with strife" (Prov. 17:1).

Cannon says: "In my earliest observations on the stomach I had difficulty, because in some animals peristalsis was perfectly evident, and in others there was no sign of activity. Several weeks passed before I discovered that this difference . . . was associated with a difference in sex. The male cats

were restive and excited on being fastened to the holder, and under these circumstances gastric peristalsis was absent; the female cats, especially if elderly, submitted with calmness to the restraint, and in them peristaltic waves took their normal course" (1911[a], p. 217).

Somewhat similar observations were made by Cohnheim (1907) and Carnot (1907); the latter used dogs with a very small duodenal fistula and found that the slightest uneasiness, excitement, or fear would immediately close the pylorus and keep it closed for some time. He found its behavior altered also when there were small ulcers in the stomach or duodenum, ascarides in the small bowel, or irritating lesions almost anywhere in the intestine or abdomen. He showed, as Thomas and Wheelon did later, that spasm of the pylorus may be brought on by stimulation of almost any visceral afferent nerve. It can be produced by rubbing, stretching or crushing the urinary bladder, the ureters, kidneys, intestines, the anal sphincter, or the parietal peritoneum. As these effects could be obtained after section of the vagi in the neck, the efferent paths must be in the splanchnic nerves.

The experiments of Oser, Thomas and Wheelon, and Carlson and Litt showed that the pyloric sphincter responds to stimulation of the vagi and the splanchnics with the same mixtures of contraction and relaxation that have been observed in other parts of the tract. As usual, much depends on the condition of the muscle at the time of the experiment; if, to begin with, it is contracted, it will relax; and if it is relaxed, it will contract. Furthermore, as Openchowski showed in 1889, the effects vary somewhat in different species of animals. The one interesting point is that the pylorus seems a little more likely than other parts of the digestive tract to respond with an increase of tone to stimulation of the splanchnics (Klee, 1913). This offers some support for Gaskell's idea that the muscle in the pylorus is peculiar, but from their studies Thomas and Wheelon felt that the question was still open.

A number of workers have found that the sphincter tends to contract under the influence of adrenalin (Smith, Winkelstein and Aschner, Nakanishi), but I think little significance

can be given to such observations, especially since Shipley and Blackfan, Thomas, and Brown and M'Swiney have shown that the typical relaxation produced in other parts of the tract can often be obtained at the pylorus, if the initial tone there happens to be high. Furthermore, the stimulating effects of adrenalin can be obtained sometimes with strips of muscle from the body of the stomach (Thomas, 1926, Brown and M'Swiney, and Carlson, Boyd and Pearcy).

Stahnke has reported some interesting experiments in which he stimulated the vagus in man by putting an electrode in the esophagus. He saw at times relaxation and at other times spasm of the pylorus, sometimes retching, and not infrequently, reverse peristalsis in the duodenum, which pushed food back into the stomach.

THE EFFECTS OF ULCERS

When ulcers are present in the neighborhood of the pylorus they act not so much by affecting the acidity of the gastric contents as by causing spasm or actual cicatricial closure of the opening. When the ulcer is near the pylorus the effect is probably a direct one of the inflamed tissue on the underlying muscle; when it is high up in the stomach and still causes slow emptying, it may be that the tone of the whole organ has been raised by irritation, and that the sphincter shows the spasm most strikingly because it is most sensitive. It may be also that there is a weakening of gastric peristalsis, a change in the conduction of the waves as they approach the pylorus, or a second unrecognized ulcer near the sphincter.

The initial rapid emptying seen with some cases of duodenal ulcer is due probably to the marked increase in the tone of the stomach and in the depth, intensity, and number of the gastric waves. This activity tends to push the material rapidly into the bowel. Later, when most of the food has left, and the stomach has lost that stimulus to contraction, the spasm at the sphincter due to the ulcer, or the hypertonicity of the inflamed duodenum often delays the egress of what remains.

An initial rapid emptying of the stomach in some cases of carcinoma of that organ may be due to a contraction and stiffening of the longitudinal muscle which causes it to pull on the pylorus and to hold it open. It may also be due to the achlorhydria which so often leads to a rapid emptying of the stomach. That is supposed to be due to the fact that the gastric contents do not then stimulate the duodenum enough to close the pylorus, but doubt has been cast on this theory by the observation of Palmer (1927) that in such stomachs a highly acidified barium meal will leave just as rapidly as a neutral one.

THE EMPTYING TIME OF THE STOMACH

Many years ago, when the stomach was looked upon as the organ of digestion, it was customary to estimate the digestibility of a food by the length of time it took to pass into the bowel, and lists containing such data can be found in most of the older books on physiology. Now that we know that the main organ of digestion is the small intestine, and that attempts to spare the stomach only throw more work on the bowel, we are not so much interested in such lists, but the figures on which they are based doubtless have some clinical significance, and later, when we know better how to interpret them, we may appreciate more highly those gathered by Beaumont, Penzoldt, Fermi (1901[a]), and Hawk and his associates (Hawk, Rehfuss and Bergeim).

PYLORIC STENOSIS IN INFANCY

There are some interesting physiologic problems connected with the congenital pyloric stenosis of infancy. As is now well known, these infants do badly on liquids and sometimes get well when fed with semisolids (Sauer). It has already been shown that solid foods increase the tone of the stomach more than liquids do, and it may be that the peristaltic waves are then deeper, more frequent, and more capable of pushing the gastric contents into the bowel. It may be, also, that the waves can grip solids more easily than fluids.

It is interesting also that these infants promptly get well and stay well after the Fredet-Rammstedt operation, which consists of cutting the sphincter across down to the mucous membrane (Wollstein, and Veeder, Clopton and Mills). Subsequent explorations or necropsies indicate that after this operation the muscular tumor disappears, but it does not seem to do so after the making of a gastroenterostomy (Lewis, D. and Grulee). After the Rammstedt operation, the resultant scar tissue pulls the ends of the muscle together and welds them into a practically normal sphincter which, so far as we know, serves the child satisfactorily for the rest of its life.

An interesting attempt to explain these pyloric hypertrophies of infants on the basis of a reversion to a type of sphincter found in the edentates has been made by Wernstedt.

SUMMARY

It has been shown that at the pylorus there is a fibrous barrier between the muscle of the stomach and that of the duodenum, a barrier that accounts for the separation between the peristaltic activities on the two sides. This barrier is not complete and some rhythmic influences run over it in both directions.

The anatomic and physiologic peculiarities of the first portion of the duodenum have been described. It is still a question whether or not every wave pushes a little material into the cap, but most of the evidence seems to be against the view that it does.

The possibility of an acid control of the pylorus was seen in the early eighties, but even then there were a good many difficulties in the way of accepting that view. Although doubts remain on some points, it seems certain that the presence of any substance that in any way stimulates the upper bowel will delay the emptying of the stomach. On the other hand, anything that stimulates the activity of the stomach will cause it to empty faster; hence we can say that there is a dynamic balance between the two viscera. We do not know yet just how the retardation of emptying is effected, but it

seems to be due to several factors, among which the contraction of the sphincter is probably the most important. That it is not all-important is shown by the fact that the stomach continues to empty fairly normally after excision of the sphincter.

It is doubtful whether any chemical stimulus is needed on the gastric side to open the pylorus. It relaxes at intervals just as the antral muscle, of which it is a part, relaxes, and if the gastric contents are then under any pressure the liquid part is squirted out as if through a sieve with one hole, and the more solid parts are retained.

Hydrochloric acid is one of the substances which, in strong concentration on the duodenal side, closes the pylorus. Whether, in the chyme coming through the pylorus, it is normally present in sufficient amounts to have much effect, is still uncertain. We probably have no more right to speak of an acid reflex than of a fat, a food, or an osmotic pressure reflex. Much evidence suggests that the differences in the rates at which different foods leave the stomach are due largely to differences in their solubilities in gastric juice. The progress of material through the pylorus is also under the control of nervous influences.

No discussion of pyloric function is complete without reference to the fact that at a certain stage of digestion, duodenal contents run backward into the stomach and serve to neutralize any excess of acid there.

One of the important factors determining whether or not a gastric wave forces food through the pylorus may be the way in which that wave approaches the sphincter. Those that travel deeply and peristaltically right to the end would seem to be more likely to push material through than those that travel shallowly, or those that apparently block themselves by ending in systoles (Chapter XIII). It is suggestive, also, that a part of the longitudinal muscle-layer of the stomach dips down into the center of the circularly arranged pyloric bundle in such a way that when it contracts it must tend to widen the opening. If the longitudinal and the circular fibers were always to contract at the same time, the circular ones, being much stronger, would probably keep

the opening closed, but if at times the actions of the two layers were to be dissociated, and my records show that they often are, the shortening longitudinal muscle might, from time to time, find itself unopposed.

In diseased stomachs the spasm of the pyloric muscle due to nearby ulceration, or the narrowing due to the presence of scar tissue or of cancer cells, has much more to do with gastric emptying than has the acidity of the gastric contents.

CHAPTER XVIII

THE MOVEMENTS OF THE SMALL INTESTINE

As soon as physiologists began to study the intestine with the animal opened under salt solution, they saw that there were at least three main types of activity: the rhythmic segmenting movements, the swaying or pendulum movements, and the peristaltic rushes.

Rhythmic Segmentation. This is brought about by localized rhythmic contractions of the circular muscle, generally in the duodenum and jejunum: contractions which knead

Fig. 59. A photograph of the small intestine during rhythmic segmentation. (*From Cannon.*)

the intestinal contents, mix them with the digestive juices, and spread them again and again over the absorbing surface of the mucous membrane. According to Cannon, this is the most common and most interesting process to be seen in the small bowel. "A mass of food is seen lying quietly in one of the . . . loops. Suddenly . . . constrictions at regular intervals along its length cut it into little ovoid pieces. A moment later each of these segments is divided into two particles, and immediately after the division, neighboring particles rush together . . . and merge to form new segments. The next moment these new segments are divided, and neighboring particles unite to make a third series, and so on."

With the animal open under salt solution the process is not quite so regular as that which Cannon describes, and it is impossible to say why indentations appear first in one spot and then in another. This kneading process will continue in one place for a half hour or more, without causing much if any downward progress of the material, and then the loop will either quiet down for a while, or a rush wave will come along to carry the contents onward into the lower bowel.

In the cat, Cannon found that the rate of these contractions was usually between 18 and 23 a minute; in the white rat there were from 44 to 48 a minute; and in the dog there were two rates: one like that of the cat, and the other between 12 and 14 a minute. He never saw segmentation in the rabbit, but I have seen it on two occasions.

Pendulum Movements. In the rabbit, and to a certain extent, in other animals and man, a local mixing of the intestinal contents with digestive juices, similar to that produced by the segmenting contractions, is brought about by swaying or "pendulum" movements, during which the contents of a short loop are thrown from one end to the other. Sometimes it looks as if the bowel were being drawn over its contents like a stocking over a foot. The rate of these movements is probably the same as that of the segmentations, and as was seen in Chapter VII, it is generally graded from some 20 per minute in the duodenum to perhaps 10 per minute in the lower ileum.

Dr. Zimmermann and I have discovered recently, on measuring successive pictures in a motion picture film, that some of the contractions which we had thought were purely pendular in nature had really been traveling intermittently down the bowel. Just how far they go we cannot yet say. We have also been able to show that the statement usually found in textbooks that the circular and longitudinal muscles contract together (Bayliss and Starling, Gayda) is not necessarily true; in many of our pictures there is little sign of a correlation between the activities of the two sheets. Sometimes the contractions are quite different in form and rate, and at other times they are similar but slightly out of phase, as was found by Trendelenburg in the guinea pig

(1917, p. 67). On the basis of some interesting embryologic work, Carey (1921) has suggested that the movements of one coat should always be slightly ahead of the other, but a good deal of research must yet be done on the physiologic side of his theory before we can properly appraise its value.

Peristaltic Rush. Most of the forwarding of the intestinal contents is brought about by large waves which, from time to time, run down the bowel. These may arise in any part of the small bowel and may run either short or long distances; in diarrheic rabbits I have seen them go from the pharynx to the anus. The classic article on the subject is by Meltzer and Auer who introduced the term "peristaltic rush." These rushes have been referred to also as diastaltic waves, rollbewegungen, and schubbewegengen.

In 1913 I obtained the first graphic records of rushes as they passed six recorders attached to different parts of the bowel, and since then Miss Mahoney and I have studied the subject in considerable detail. No exact information could be obtained about these waves so long as observers had to content themselves with watching them pass; too many things happen at one time, and besides, there are slow changes in tone, and small rhythmic movements that cannot be seen until they are enlarged and recorded. Rabbits seem to be the most satisfactory animals in which to study these waves; some show several in an hour while others show only a few during a day.

The easiest way in which to start them is to get the animal to drink or to swallow, either by putting a little water into the pharynx or by tickling the fauces. This point might be remembered by surgeons when they are trying to start up peristalsis after operations. In the light of our findings in animals, the surgeon's usual policy of withholding fluids and preventing swallowing would seem to be highly undesirable and designed to produce just the situation that he most fears. This statement of course does not refer to those cases in which, on account of the presence of suture lines or patches of peritonitis, peristalsis is not desired.

Origin of the Rushes. As soon as graphic records of these rushes were obtained, it was noted that many of them, or

about 55 per cent, appeared in the duodenum about the time that a gastric wave reached the pylorus. So far as I can see, there is nothing peculiar about the appearance of these waves that start rushes, but something may be learned later. Not infrequently, after the departure of a rush, the stomach seems to be inhibited for a while, and this may sometimes be seen even when the rush starts low in the bowel. It is interesting to find that Van Braam Houckgeest, who first described these waves in 1872, made note of the fact that they sometimes begin in the stomach.

Apparently the stomach does not have to empty any of its contents into the duodenum in order to start these rushes; in fact, as was pointed out in Chapter XVI, the duodenal tonus contractions from which they seem to originate generally appear a few seconds before the gastric waves reach the pylorus. Sometimes another rush will start a few seconds later, when the stomach discharges some of its contents into the bowel, and that probably accounts for the fact that a few of the rushes that Miss Mahoney and I recorded had two crests. Occasionally in man, when the stomach is emptying rapidly, the wave on the antrum will seem to run right on down the duodenum with the barium. It must not be assumed from this that the filling of the duodenum always starts a rush, because it often does not.

As already mentioned, many of the rushes seem to begin in swallowing movements, but others can be started by stimulating the duodenum. At times, after the duodenum has been segmenting actively for a while, it seems to get on a hair trigger, and a slight pinch will start a rush. After that, for a while, no more rushes can be started, and the bowel seems to be fatigued or refractory.

My kymographic records show clearly that rushes can begin anywhere in the bowel. What usually happens is that a loop fills from above; perhaps a rush stopped there, or one may have dropped some material as it passed onward, or material may have just seeped in. The tone of the loop rises and the amplitude of its rhythmic contractions increases; the material within is thrown backward and forward more and more forcibly by the two ends of the loop, and from time

to time the bowel will seem to try to empty itself. This behavior is so characteristic that my assistants and I speak of such a loop as "trying to start a rush"; it either finally succeeds, or else it gives up and quiets down. Usually a ripple or rush will come on down from the stomach to upset the balance or to give the necessary impetus, or the balance may be disturbed sufficiently by the emptying of a loop lower down, or by movements of defecation. Generally there are a number of such loops filled and active and corresponding somewhat to runners on the bases of a baseball diamond: when one moves they all tend to shift downward a base or two, and then they have to wait for a while. Thus, "by a combined process of kneading and peristaltic advance, the food is brought to the ileocolic valve" (Cannon, 1911[a]).

The peristaltic rushes do not always carry the intestinal contents along. They may carry them for a way, and then drop them, only to pick up some material farther down. This phase of the subject has been discussed more at length in Chapter VI.

Stopping the Rushes. My graphic records show that often when some disturbance is passing along the bowel a rise in tone will take place almost simultaneously in many parts of the tract. These disturbances probably travel by way of the nerves either in the bowel wall or in the mesentery; they can jump some regions to appear in others, and they probably enable the digestive tract to act as a unit.

Most of the rush waves in the rabbit's small intestine stop in the lower ileum, but some go on down the colon, and not infrequently in passing, they give rise to contractions of the cecum. When the rush waves stop in the lower ileum they either fade out in this sluggish part of the bowel or else are blocked by powerful contractions or by a marked rise of tone. In one instance, motion pictures of a rush showed clearly that it struck the closed ileocecal sphincter with such force that it was reflected and caused to run back up the bowel for some 20 or 30 cm. Dr. Child tells me that he has often seen a similar reflection of waves at the ends of the rows of swimming plates in certain Ctenophores. One of the most important functions of the ileocecal sphincter and of the slight

rise in the gradient of rhythmicity leading up to it is probably to stop the rushes; and it is doubtless fortunate for us that so many are thus stopped, because otherwise we might soon die of starvation and diarrhea.

Influence on the Brain. An interesting feature about the rushes is that they seem to affect the brain quite markedly even when the animal is well under an anesthetic, and when the only path from the bowel is along the vagi. Often as the rush begins, or as it proceeds down the bowel, there is a deep sigh and, not infrequently, a slight struggle. This is of interest because patients are sometimes distressed by the powerful and frequent rushes of diarrhea: they feel queer, sweat breaks out on them, and sometimes they faint at the toilet. The rushes that take place in health do not bother us, and with the roentgen ray I have often seen them whisking down the jejunum without affecting in any way the consciousness of the subject. At times they can be recognized by the gurgling sounds that they make as they traverse the gut.

Rate of Travel of the Rushes. When they first start, they travel usually from 2 to 4 cm. a second, but since they travel faster the farther they go, by the time they reach the lower ileum they are often covering from 7 to 25 cm. a second (average 10 cm.). The mean rate of some sixty-five rushes that went from one end of the bowel to the other was 6.5 ± 1.8 cm. a second. There were, however, two modes to the distribution curve: one about 4.5 cm. and the other about 9.5 cm., and most of the data were grouped between 3.5 and 6.5 cm. As was to be expected, the rushes showed a tendency to slow up before they were brought to a stop (Alvarez and Mahoney (1924). According to the gradient theory, when a rush travels orad it should go more slowly because, in a way, it must travel up hill; actually I did find that to be the case.

These rush waves seem to travel somewhat as a spark might sweep along a fuse in which the physical and chemical characteristics of the powder are so graded that the combustion can proceed more easily in one direction than in the other. From the gradient theory, we should expect the rushes to travel fastest in animals with the steepest gradients, and Miss Mahoney and I obtained some evidence pointing in

that direction, but not enough to satisfy us. Similarly, we thought that purged animals, with perhaps a steepened gradient of activity in the bowel, might have more and faster rushes, but in some experiments in which tincture of aloes was given we could not show it. Perhaps we would have had more success with another type of purgative.

According to the theory, any irritation of the bowel that will raise the lower end of the basic (metabolic?) gradient

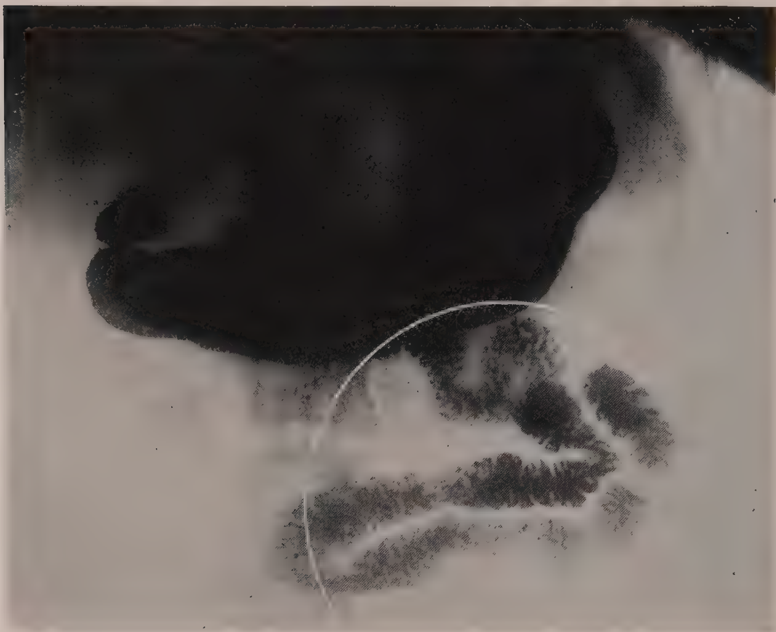

Fig. 60. The characteristic appearance of a barium meal in the first loops of jejunum. (*From L. G. Cole.*)

should slow the rush waves and finally stop them. Thus it was interesting to find that in a large series of experiments in which mild degrees of dynamic ileus were produced in rabbits by injecting a few drops of dilute phenol or turpentine into the muscle of the lower ileum, rushes were either absent or else hard to start. The injections were made under ether anesthesia, and after from twenty-four to seventy-two hours

the animals were opened again and observed in the tank of warm Locke's solution.

Activity in the Small Bowel of Man. It is easy to see with the roentgenoscope that to and fro movements, rhythmic segmentations, and rush waves occur. So far as I can tell from watching them, the rate of travel of the rush waves is about the same in man as in rabbits. As in the animals, so in man, they are very likely to appear immediately after taking food; and with diarrhea, they are likely to rush right on to the anus where they produce a call to defecation. Every pediatrician must often have wished, while struggling with the problems of diarrhea in infants, that he could keep them from eating for a few days, because so long as they fast they are all right, but the moment they eat, the rushes begin. We all know that the best time to look for the rushes that lead to defecation is in the morning after breakfast, when the bowel has been quiet for some time, and when, as has already been pointed out, the mechanism seems to have gotten on a hair trigger.

One of the most characteristic things about the small bowel in man is the fact that the food whisks rapidly through the upper jejunum and travels more slowly in the lower ileum. This is quite apparent in Figures 60 and 61. In the jejunum the barium mixture seems to have been sprayed over the tops of the valvulae conniventi; and as Milani (1923) says, it looks somewhat like snow on the branches of an evergreen tree. Actually, the word "jejunum" comes from a Latin term meaning hungry, and it was doubtless given to this section of the bowel by the older anatomists because it was generally found to be empty (note old German "leerdarm"). It is only in the lower ileum (the word comes from a root meaning twisted) that the progress of material is slowed to such an extent that the barium can gather into dense sausage-like masses.

I have not been able to satisfy myself that there is a gradient in the rate of rhythmic contraction down the small intestine of man, but I have not yet had time to do much work on the problem. On many occasions I have, with the roentgen ray, been able to count about 10 waves per minute in the

duodenum or jejunum, and similar observations have been made by others (Hurst, Milani). In 1914, I recorded the contractions of the bowel in a man who was being fed

FIG. 61. Shows the feathery appearance of a barium meal in the jejunum and the dense masses that accumulate in the terminal ileum (in the circle). (*From L. G. Cole.*)

through an enterostomy opening, made to hasten the healing of an ulcer of the stomach. Actually this ulcer did heal rapidly under the treatment, so that the man was in fair health during

much of the time covered by my studies. I put a little recording balloon through the fistula and sometimes let it pass down 2 meters or more into the ileum. The rate of the

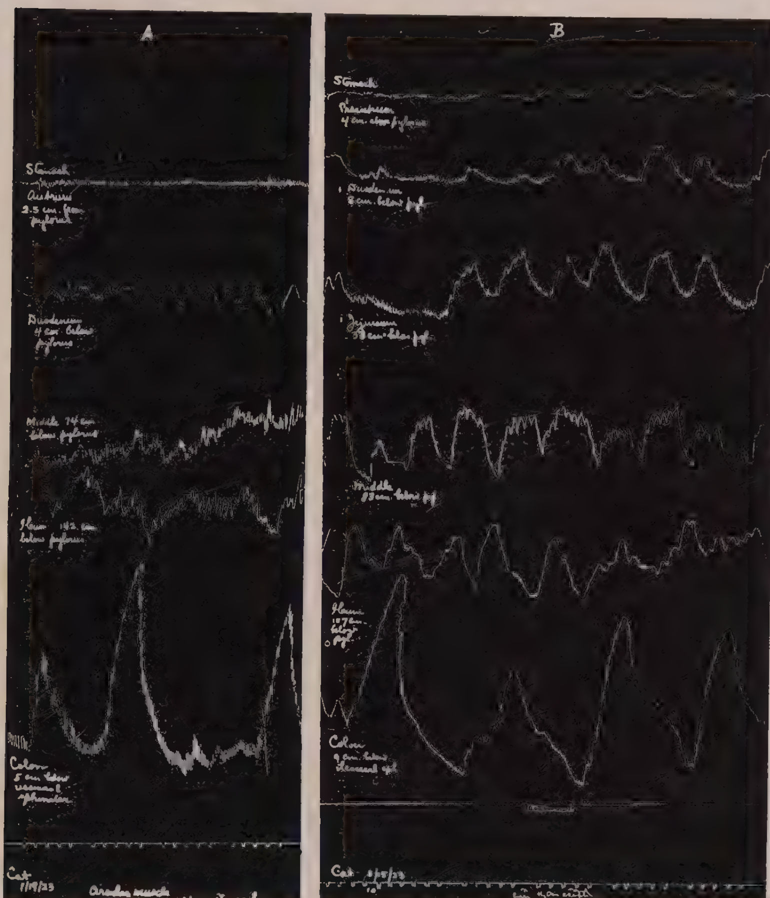

FIG. 62. Tonus waves in the bowel of the cat. The small rapid excursions of the levers were due to the respiration.

rhythmic contractions varied usually between 9 and 11 a minute no matter where the balloon was, but sometimes, during the height of digestion, it rose to 14 a minute in the jejunum and once dropped to 7 in the ileum.

Similar experiments on normal young men have been made by Daniélopolu, Simici and Dimitriu who found 10 contractions a minute, apparently in all parts of the bowel, as they make no mention of a gradient. Rieder (1925), however, who has made a careful roentgenologic study of the movements of the small intestine, says that in the ileum they are definitely slower and less frequent than in the jejunum. I once saw from 7 to 9 "pendulum" movements a minute in a woman with a large umbilical hernia which enabled me to watch peristalsis through a thin layer of skin, but unfortunately I could not tell whether I was dealing with jejunum or ileum. Further work is needed on the problem.

From the difference in the appearance of the barium shadows in jejunum and ileum I think there can be no question about the existence of a gradient of irritability down the bowel of man. The jejunum is so sensitive that it responds actively to the presence of food while the ileum lets it lie quietly for long periods of time. I have shown this in human subjects with balloons as well as with food.

The Tonus Rhythm. Tonus waves seem to have a good deal to do with the progress of events in the digestive tract, and time and again I have seen them apparently involved in starting and stopping the rush waves. Their appearance in the graphic records is well shown in Figures 62 and 63. They do not seem ordinarily to travel along the bowel, but it is possible that they do so under abnormal conditions, as in the case of intestinal obstruction. In animals with intestinal obstruction, I have seen slowly moving, deep peristaltic waves which were different from anything I have observed in health. It is interesting to note that just as in the stomach, so here in the bowel, we find one bit of muscle responding at the same time to a local segmenting rhythm, a slower tonus rhythm, and a traveling peristaltic wave.

The Passage of Fluids without Peristalsis. There is another point which is not generally recognized, and that is that liquids will run long distances through the small bowel without the help of any peristaltic contractions. (Marbaix, 1898, p. 271, Müller and Kondo, p. 335, Alvarez and Mahoney, 1924.) Unfortunately this mechanism fails when there is

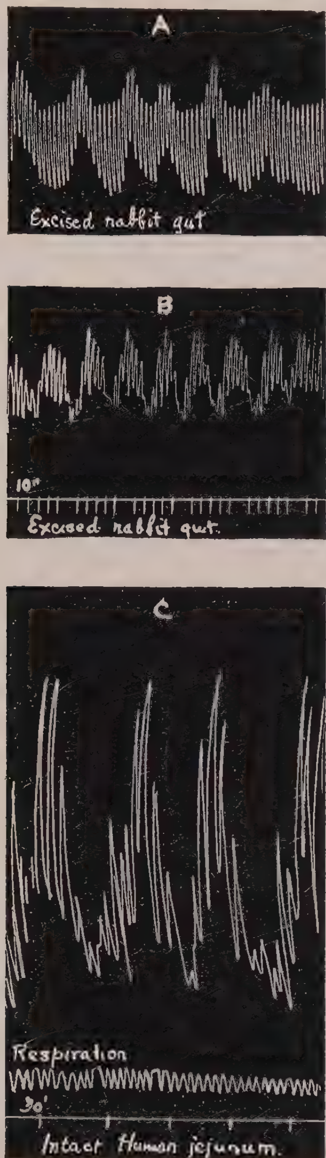

FIG. 63. Tonus waves observed in records obtained from excised segments of rabbits' bowel and in a record made with a balloon passed into the jejunum of a man.

much gas present to distend and kink the bowel, as in cases of paralytic ileus. I have commented elsewhere in this book on the great clinical importance of the fact that liquids can seep through the tract in either direction, past obstructions, and through parts of the tract where the gradient of forces is reversed. Solids cannot do this; hence, when parts of the tube are irritated, diseased, or weakened, it is well to give the patient a smooth, residue-less diet such as is described in Chapter XXIV.

Colic is due probably to an incoordinated type of peristalsis which results in pressure being put on a segment of bowel by contractions above and below.

Reverse Peristalsis. As has been pointed out in many places in this book, reverse peristalsis is not an impossibility in the small bowel, but it can hardly be called normal, unless perhaps in the terminal ileum, when the bowel is trying to stop oncoming rushes, and in the upper duodenum, when material is being thrown back into the stomach.

Factors Stimulating Peristalsis. The work of Carnot and Glenard with perfused intestines convinced them that the main factor in increasing the activity of the bowel is an increase in the rate of blood flow through the muscle. It is probable, therefore, that some of the increase in the activity of a loop of digesting bowel is due to the increase in its blood supply, and that means that the vasomotor nerves to the bowel are probably very important. Unfortunately, we know almost nothing about their behavior, but some information can be found in an excellent article by Hotz (1909). The theory has been advanced that cholin is the normal hormone for peristaltic action but that will probably be hard to prove (see Magnus, 1925). It certainly stimulates peristalsis and it may turn out to be a helpful drug in cases of paralytic ileus.

Is the Duodenum Indispensable? Some observations made in the course of studies on the rapidly fatal type of high intestinal obstruction led physiologists to suspect that the duodenum might have some function that makes it indispensable to the body. That this is not so was proved by Mann and Kawamura who removed the entire duodenum

from a number of domestic animals and then kept some of them in good health for two years or more. The only difficulty was that in two of the dogs there developed a jejunal ulcer just outside the stomach.

Peristalsis and Peritonitis. The surgeon is particularly interested in the function of the bowel that has become paralyzed and distended. At what point does the vicious circle begin? What is the influence of peritonitis? When does the damage to the contractile power of the muscle become irrevocable, and what can be done to start up normal peristalsis again? These are some of the questions that must be answered.

Unfortunately little information is available. The only extensive article that I know of on the subject is the one by Hotz. He recorded the activity of intestinal loops drawn out through an opening made in the abdominal wall. He produced peritonitis by opening the animals and cutting the small bowel across, and twenty-four hours later he reopened the abdomen and pulled out a small loop for the recording of contractions. In this way he found that loops of bowel covered with inflamed peritoneum were as active as normal controls. If, however, in addition to peritonitis, he produced an obstruction of the upper part of the bowel, he found later that the distended loops showed only a few weak movements. He concluded, therefore, that it is not the peritonitis which damages the intestinal muscle but the distention that accompanies it.

In the presence of peritonitis the intestinal vessels are greatly distended with blood, and Hotz came to the conclusion that this may even improve the activity of the bowel. My experiments agree with his in showing that when the bowel is distended or the circulation damaged, the pendulum movements fail first and the tonus contractions and the peristaltic waves last.

Hotz found that after section of the splanchnics the animals did not tolerate much further operative work, and were so sensitive to peritonitis that they died in a few hours after the soiling of the abdominal cavity. He came to the conclusion that in the later stages of peritonitis the splanch-

nics are badly damaged by toxins because the bowel behaves as it does when they are cut. The muscle fibers and Auerbach's plexus survived as long as there was no distention, and in some cases he saw the intestinal loop contracting beautifully even after the serosa was covered with a thick purulent exudate. In severe peritonitis the influence of vagal stimulation can no longer be shown, and any changes in intestinal activity brought about by stimulation of the splanchnics are due, he thinks, to resultant changes in the circulation of the wall of the bowel.

Ecker and Rademaekers (1926) have begun some interesting studies which will probably throw light on the way in which filtrates of the cultures of certain bacteria, when injected intravenously, produce diarrhea.

An excellent study on the adaptation of the structure of the intestinal blood vessels to their function has been made by Mall (1896[b]).

CHAPTER XIX

THE ILEOCECAL SPHINCTER

In the following discussion I shall use the term sphincter in preference to valve because all those who have observed this structure in the living, unanesthetized, human subject have emphasized the fact that, under those conditions, the valvelike lips which are so obvious in the dissecting room are not to be seen, but in their place is a domelike papilla with a dimpled orifice at the summit (Fig. 65).

Observations on Man. Rutherford, Macewen, and Short have all made interesting physiologic studies on patients with fistulas into the cecum. Looking through the opening, Rutherford saw a papilla about 1.8 cm. in diameter, projecting about 1 cm. from the wall of the cecum; the mucous membrane covering this eminence was smooth and glistening, and had a red color much deeper than that of the surrounding cecal mucous membrane. Radiating from the little opening in the summit of the papilla were five small folds which ran out about 6 mm.

From time to time there appeared rhythmic changes in the height and width of the papilla, and swaying movements, which were associated with the to and fro contractions of the terminal ileum. With each enlargement of the eminence there came a relaxation of the circular fibers; and some semifluid feces, about 4 c.c. at a time, would run into the cecum. Under the influence of excitement, these little jets would appear as often as once every second or two.

There was no appearance of a valve until the patient was placed under deep anesthesia; then the papilla relaxed, it became more and more oval and changed into a slit 2.5 c.m. long. Normally the sphincter was so tight that even a No. 12 English catheter could not be passed; the failure was due partly, however, to the production of pain which caused the experimenter to stop before he had achieved his object.

Macewen had a similar patient in whom he watched the behavior of the sphincter. He was particularly impressed

with the sudden increase of activity which occurred after the taking of food, the increase in the flow of mucus at that time, the flow of fluid out of the lumen of the appendix just before material came through the ileocecal sphincter, the

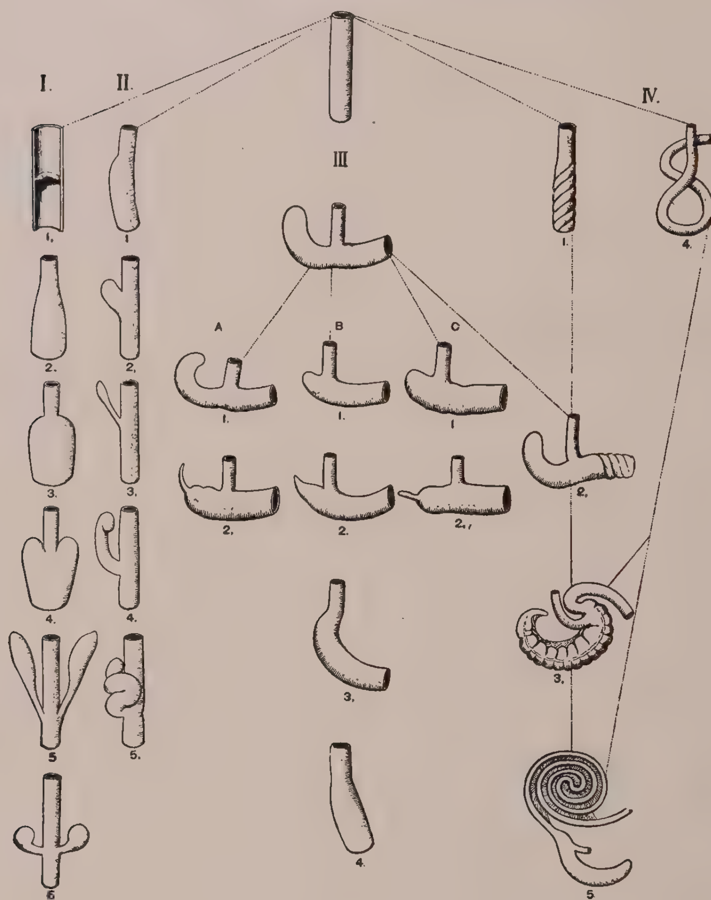

FIG. 64. Vertebrate types of ileocolic junction. (*From Huntington.*)

jetlike emptying of the terminal ileum, and the dryness of the mucous membrane of the cecum that appeared one day when the patient's digestion was upset by the receipt of bad news.

In Short's patient, the tone of the ileocecal sphincter was not so good as it was in Rutherford's, and instead of being perfectly round the papilla was somewhat oval. Furthermore, when digestion was in progress, and jets of ileal contents were coming at frequent intervals, the sphincter remained quite relaxed and had the appearance of a slit about 3 cm. long. He was then able to pass his finger into the ileum without producing pain. In spite of this occasional slit formation, Short still felt that the opening "should rather be regarded as a sphincter than a valve." He noticed that the coils of ileum were always active, but when the patient was fasting, and lying quietly on his side, nothing came through the opening for hours at a time; then food would be taken, and within from one and one-half to four minutes there would appear little gushes, first of succus entericus and later of food residues: about 15 c.c. every half minute or so.

THE FUNCTION OF THE SPHINCTER. The purpose of the ileocecal sphincter is, first, to prevent the reflux of foul, bacteria-laden feces from the colon, where absorption is slight, into the ileum where absorption is good; and second, to prevent too rapid a passage of food through the last segment of the small bowel. In this second function of holding back material coming down through the lower ileum, the sphincter is doubtless helped by contractions arising in those muscle fibers that reinforce the wall in the last few centimeters of the intestine. This accessory sphincter, which has been described by Luschka, Keith (1903), and Elliott (1904), acts probably much like the bands of highly rhythmic muscle that take the place of definite sphincters in some of the lower forms of life (Bottazzi, 1898, and von Brücke, 1905, p. 202).

In the rabbit, the sphincter is surrounded by a muscular organ called the sacculus rotundus. As I showed years ago, this not only tends to contract with a rate a little higher than that of the muscle in the lower ileum, but, in the last 25 cm. of the bowel, there is generally a gradient of rhythmicity extending upward toward the ileocecal sphincter (Alvarez, 1915[a]). The result is that peristalsis tends to be reversed in

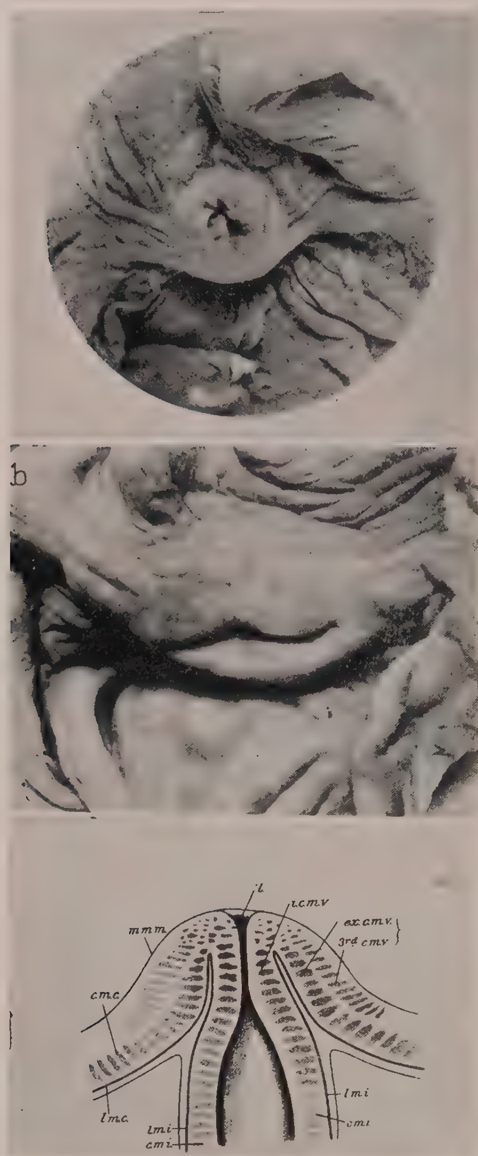

Fig. 65.

this segment, and material cannot pack up against the sphincter quite as hard as it otherwise would.

Perhaps most of the rush waves down the small bowel are stopped in the terminal ileum, but in the rabbit it can be seen that some of them run on down the colon. On studying our motion pictures of a rush wave in a rabbit, Dr. Zimmermann and I found that it had been reflected at the sphincter and caused to run backward 25 cm. or more up the ileum. Dr. Child tells me that he often sees a similar reflection of waves at the end of one of the rows of swimming plates in a Ctenophore.

If it were not for the presence of the ileocecal sphincter, our nutrition might suffer and we might more often be bothered by diarrhea; and if the colonic contents were to flow back into the ileum we should expect to see symptoms of true intestinal autointoxication, whatever they may be (Alvarez, 1924[b]). Actually it is interesting to note that when an ileal fistula is made in an animal or man, the bowel after a time succeeds somehow in slowing the progress of its contents and in dehydrating them so that they come to look more like feces (Beuttenmüller).

THE REASON FOR THE BLOCKAGE OF WAVES AT THE ILEOCECAL SPHINCTER

In many ways the conditions at the ileocecal sphincter resemble those at the pylorus: again there is a barrier, not only between the contents of the two portions of the tract, but also between the peristaltic waves on the two sides; again this barrier between the activities on the two sides is not complete; and again it appears to be due mainly to a folding of the muscle layers and an interposition of connective tissue. As can be seen from the descriptions and illustrations of

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FIG. 65. A, Papilla of ileocecal sphincter from a man dead twenty-four hours. B, a similar papilla, more relaxed and valvelike. C, diagrammatic illustration made from a section through the papilla. C.M.C. = circ. muscle of cecum; C.M.I. = circ. muscle of ileum; L.M.C. = longit. muscle of the cecum; C.M.I. = longit. muscle of the ileum; I.C.M.V. = int. circ. muscle coat of the valve mammilla; EX.C.M.V. = ext. circ. muscle coat; 3rd C.M.V. = third circ. muscle coat. (*From Rutherford.*)

Luschka, Lebon and Aubourg, Toldt, Engelmann and Van Brakel, Elliott (1904), and Rutherford, the layers of circular muscle from the ileum and colon run out to the ends of the two lips which, in the dead subject, resemble the leaves of a valve, and between them runs a layer of longitudinal muscle. Apparently there is not the discontinuity of the fibers which is to be seen at the pylorus, but it is highly probable that the folding of the muscle layers accomplishes the same purpose by leading approaching waves into a blind pocket and losing them there (Fig. 65).

Just as at the pylorus, so here, the blockage of the waves may be ascribed also in part to differences in the muscle above and below the sphincter, and even to peculiarities in the sphincter itself. The muscle in the colon appears to be more sluggish than that of the ileum, and its rhythmic activities are different. There are signs also, pointing to a greater irritability of the sphincter muscle which enables it to contract a little ahead of its turn. If a cat's colon is tied off at the rectum and filled with soapy water, it will contract powerfully in its efforts to empty itself. Under such conditions I have seen deep reverse waves which looked for a moment as if they were surely going to force material into the ileum, but suddenly the sphincter contracted down into a hard white knot, and the advancing wave either faded out or broke ineffectively against the barrier.

According to Bayliss and Starling (1900, p. 109), in the dog, waves often run from the ileum onto the colon, but in that animal the two segments of the tract meet end to end without much sign of a division between them.

Control of the Sphincter. Tönnis cut all the nerves going to the ileocecal region and found that the sphincter was paralyzed for only four or five days. He concluded, therefore, that like the rest of the digestive tract, it is largely autonomous, and dependent on the nerves only for regulatory impulses. He found also that if any section of the ileum was anastomosed with its end to the side of the colon, the new opening would take over quite satisfactorily the function of the sphincter. That is what one would expect from the experience of surgeons operating on man; they too

have found that there is no disturbance in health after the making of anastomoses between the ileum and the colon.

Tönnis studied dogs with fistulas into the ileum and colon a few centimeters above and below the sphincter. Normally, material came through at intervals of from six to thirty seconds. Changes in the temperature of the fluids injected had no influence on the rate of passage; and he could see no difference in the behavior of the sphincter after putting N/10 HCl or NaOH into the colon. The one thing that did put a stop to the opening of the sphincter was the filling of the colon with feces. That this is not so effective in man was shown by Donaldson, who found in 4 subjects that the small bowel continued to empty into the large even when defecation was restrained voluntarily for four days.

Short could not inhibit the emptying of the sphincter in his patient by putting acid or alkali into the cecum. He could slow the emptying by pinching the cecum but he could not stop it. Heile, Cannon, and White found also that they could slow the progress of material through the sphincter by irritating the colon, or by distending the cecum with a balloon. Conditions seem, therefore, to be somewhat similar here and at the pylorus and, for that matter, everywhere else in the bowel. As I have pointed out before, the law seems to be that stimulation at any point tends to hold back the progress of material coming down from above.

Extensive observations on a patient with a cecal fistula were made by Beuttenmüller. In her patient the mucous membrane of the cecum was insensible to pricks and to strong faradic stimulation. Her findings will be discussed at greater length in Chapter XXII. Babkin (1914, p. 374) speaks of the observations of Strashesko who, working with dogs with fistulas into the ileum and colon, noticed a marked difference between the sensitiveness of the mucous membrane in these two parts of the bowel. When he put solutions of sodium carbonate, hydrochloric acid, glucose, sucrose, and other substances into the ileum, the dog became very uneasy, it breathed rapidly, and sometimes it retched, but when these substances were put into the colon the animal failed to perceive them in any way.

The Gastroileac Reflex. So far as I know, Macewen was the first, in 1904, to call attention to the great increase in the rate of passage of the ileal contents into the colon that is seen when food is taken. This gastroileac or gastrocolic "reflex" was rediscovered by Hurst in 1913, and it has since been seen by all those who have taken the trouble to look for it. The fact that food put into the stomach through a fistula does not have much effect on the ileocecal region caused Welch and Plant to suspect that the reflex may arise in the duodenum, and also that it is dependent upon the psychic rise in tone that comes when food is eaten with relish. There is some evidence also to show that if, on account of inflammation in the cecum or appendix, the progress of material in the terminal ileum is delayed or stopped, there will be a slowing of the progress in the duodenum. This is discussed more at length in other chapters.

Lyman has described a receptive relaxation of the colon, preparatory to the arrival of ileal contents, similar to the receptive relaxation of the cardia associated with swallowing.

The Nervous Control of the Sphincter. The classic article on the innervation of the ileocolic sphincter is by Elliott (1904). He could not see that either the vagus or the pelvic visceral nerves had any control over it. In the cat he saw no change in the tone of the sphincter after stimulation of the inferior mesenteric nerves, but there was strong, steady contraction after stimulation of the splanchnics. This fits in with Gaskell's theories about the origin of the muscle in this region (1916, p. 46), and with the fact that some observers, notably Elliott (1904 and 1905, p. 415) and Kuroda, have found that adrenalin stimulates the sphincteric muscle while it causes relaxation almost everywhere else in the tract. Similar findings at the pylorus have been discussed in Chapter XVII.

Elliott found that the tone of the ileocolic sphincter diminishes slowly after the cord is destroyed, and that it is permanently lost after the splanchnics are cut. According to Tönnis, however, some contractility returns after four or five days.

Regurgitation through the Sphincter. Cannon (1911[a], p. 156) found in his early studies on cats that if an enema is held in the colon long enough some of it will run back into the ileum. In one case he saw the animal vomit water that he was quite sure was part of the enema; moreover, it contained some round worms which were probably washed back out of the small bowel. He realized, however, that the conditions under which this regurgitation took place were abnormal, and felt that the material that reaches the colon normally through the sphincter never goes back again.

It is now well known that in perhaps 60 per cent of the cases in which a barium enema is given to patients, some of it will run back into the ileum. Although there is little doubt that some sphincters are more relaxed than others, I have always suspected that if we could get the patients to hold the enema long enough we could always make it flow back. It must also be remembered that these subjects have not only been purged the night before the examination, but they come to the laboratory without breakfast. This is probably important because Hannes found in cats and dogs with an ileal fistula that enemas always regurgitated when the animal was fasting, and never when it had recently been fed. As the ileocecal sphincter held firmly even when the animal's food was allowed to run out through a fistula made just below the pylorus, he concluded that the resultant increase in tone was of psychic origin.

The regurgitation of material that has once reached the colon from the ileum is probably rare, but it may be that we would see more of it if we were always on the watch for it, and if it were easier to distinguish definitely between masses of barium in the ileum and in the pelvic colon. Case (1914[a], 1915[c]) and Groedel have reported cases in which they saw a return of fecal material into the small bowel. In the eighteenth century, when it was the fashion to take large medicated enemas, the sphincter was apparently assumed to be competent, judging from its whimsical nickname of "le barriere des apothicaires."

Many attempts have been made to ascribe the origin of certain syndromes to an incompetent ileocolic sphincter, but,

as N. W. Jones has pointed out in his careful study of 1000 cases, it is generally hard to be sure that other, perhaps constitutional and neurotic, causes are not at work. For a while Kellogg advised operating on some of these cases to tighten the lips of the "valve," but later Case (1915[b]), who worked with him, came to the conclusion that definite incompetence of the sphincter is due generally to inflammation or obstruction in the colon, so if any operation is to be done, it had better be directed toward the relief of the primary disturbance.

Anatomy and Embryology. Figure 64, taken from Huntington's splendid work, gives an idea of the many different ways in which, in the animal kingdom, the ileum joins the colon. One of the peculiar things about this region is the presence of large masses of lymphoid tissue. In man it is massed in the appendix, in the rabbit it is in the sacculus rotundus and appendix, and in the dog, it is largely in the mesentery. In addition, there are the patches of Peyer, which are particularly plentiful in the lower ileum. It seems most probable that this lymphoid tissue is placed at this point to protect the body from invasion by microorganisms; and that is understandable when we remember that it is particularly in the cecum where, with a liquid medium and sufficient food, bacterial growth is luxuriant, and the danger of invasion of the tissues great. That the strain on the protective mechanism at this point is great is shown also by the frequency with which the lymphoid tissue breaks down, with resultant peritonitis and often death.

The embryology of the sphincter was studied recently by Beattie who found that it develops very early as a swelling of the muscle fibers. At a certain stage of development the ileocecal sphincter looks very much like the pylorus. Beattie argues that a structure that develops so early in embryonic life must be of considerable importance to the organism.

CHAPTER XX

THE MOVEMENTS OF THE COLON

The Condenser-Like Action of the Colon. Anyone who attempts to discuss the movements of the colon must first be sure to say whether he is talking about herbivorous, carnivorous or omnivorous animals, because the anatomy and physiology of the large bowel are quite different in the three groups. The meat-eating animal has little need for a colon, as digestion is practically complete in the small bowel and all that remains to be done is to retrieve the water that has been used in the chemical processes. This has been poured out by the glandular cells in the mouth, stomach, liver, pancreas, and intestine, and even when the animal does not live in a desert, it is doubtless convenient to have the liquid returned to the blood. The colon acts therefore much like the condenser of a steam engine, and judging from the amount of energy required to separate water from some forms of vegetable tissue, it must be a remarkably efficient machine. Thus, in the rabbit, the semi-fluid material that enters at the upper end of a short tube comes out at the lower end in the form of little balls, so dry that they float on water.

So far as I know, this mechanism has not yet been studied, but it should be, because disturbances in it might easily account for some cases of diarrhea. In one young woman with a mild but persistent diarrhea I could see with the roentgen ray that the feces became normally solid in the middle of the colon, but liquefied again when they reached the rectum. The need for study in this field can be seen from the fact that in a large proportion of the cases of mild, chronic, or recurrent diarrhea seen in practice the cause is unknown. Occasionally the physician can demonstrate the presence of some bacterial or protozoal parasite, of achlorhydria, or colonic ulceration, but when he cannot do that he is left without the slightest conception of the nature of the basic disturbance in function. I have seen fatal cases of diarrhea in

which even at necropsy little was learned about the nature of the disease.

In some cases of constipation there may, perhaps, be an overactivity of the "condenser" with an excessive drying and concentration of the feces. The primary nature of such a disturbance would be hard to demonstrate, however, because if the progress of the feces through the colon were to be delayed in any way, the dehydrating process would continue for a longer time, and it would be hard to say what was cause and what effect.

Herbivorous and Carnivorous Colons. On account of its limited function, the colon of a meat-eater is generally short, as compared with the small intestine, and its walls are simply and stoutly built. The eaters of grass and grain must have large reservoirs in which their food can ferment for days, so they are supplied either with a large multilocular stomach or else with a big baggy cecum and a long sacculated colon. In some of the birds the colon is twice as long as the small bowel, and in addition there are capacious ceca.

Man seems to have been designed for an omnivorous diet as is shown not only by the pattern of his teeth but by the nature and proportions of his digestive tract. The stomach is simple and of the carnivorous or omnivorous type. The small intestine is so short as compared with the body length that there can be no question about its being of a carnivorous type. In the herbivores the bowel is from 25 to 100 times the body length, while in the cat and dog it is from 4 to 8 times that length. In man, it has always been supposed to be 8 or 9 times the sitting height (comparable to the body length of an animal), but recent studies by Van der Reis and Schembra indicate, as I have long suspected, that it is generally only half of that.

Years ago I found that it was useless to try to measure the intestine in the dead rabbit, because, especially when it is cut away from the mesentery, it stretches until one can only guess as to its original length. For that matter, one cannot get absolute figures even in the living animal because the tone of the longitudinal muscle is constantly changing. Some objections may be made, therefore, even to the meas-

urements of Van der Reis and Schembra who, while collecting samples of bacteria from different parts of the bowel of

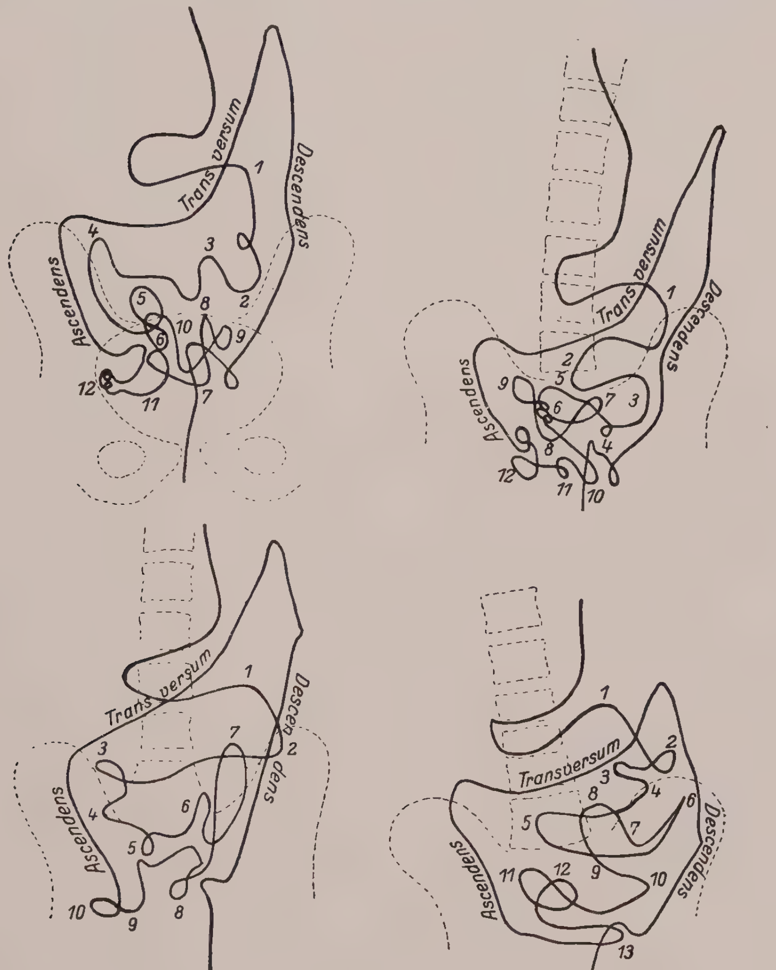

Fig. 66. Diagrams made from roentgenograms similar to those shown in Figure 49. The course of the bowel is outlined by a tube impregnated with zircon oxide. (*From Van der Reis and Schembra.*)

man, allowed a narrow tube to pass from the mouth to the anus and found that the distance was more nearly 2.5 meters

than the 7.5 that others had found in the bodies of the dead. In 12 men and women it ranged between 2.2 and 2.7 m. The straight line distance from mouth to anus, corresponding to the body length of an animal, varied between 0.50 and 0.75 m. so the proportion between this distance and the length of the bowel varied between 3.1 and 5.1. Soyesima measured the bowel during operations on 23 patients and found it ranging from 4.28 to 8.92 m., and Hess allowed a string to pass through a dog, and discovered that the bowel was 220 cm. long; after death it was 530 cm. long.

The colon of man is partly sacculated as it is in some of the herbivores, but its shortness as compared with the rest of the bowel, and the smallness of the cecum show that it was designed for the handling of only a small amount of cellulose. Actually, of course, we know that primitive man was a hunter and a fisherman for thousands of years before he became a herdsman, and it is only in comparatively recent times that he has learned to till the soil. As Darwin once pointed out, the grains and fruits preserved in the Swiss lake dwellings of neolithic times—a mere yesterday in the history of man—are so small and woody that they could not have been of much use as foods; and the people then were still dependent on the results of the chase. Even those of us who are not yet gray can remember the time when many of the fruits and vegetables now on our tables were smaller, coarser, and even less able to supply our caloric needs than they now are.

All these points and many more are ignored by the faddists and cranks who would have us return to the original "monkey diet" of fruits and nuts. Incidentally, they do not seem to know that monkeys and apes add considerable nitrogenous food to their diet by eating such things as grubs, insects, lizards, eggs, and young birds. According to Yerkes (p. 218) some of the primates "are strictly vegetarian, a few nearly carnivorous, and the majority, like man, have adopted a mixed dietary." Faddists should turn also to the article of Lieb who points out that Stefansson found the Eskimos a healthy race in spite of the fact that they live only on meat and fat. That it does not take centuries of adaptation to live

on such a diet was shown by Stefansson when he lived on it for several years and remained in perfect health.

The work of Lane and others has shown that man can get along without a colon, but that has not proved Metchnikoff's theory that he would be better for parting with it. Those who wish an entrée to the literature on this subject will find it in my article on intestinal autointoxication in Physiological Reviews (1924).

The colon, then, has several functions: in the Herbivora and Omnivora it serves as a reservoir in which cellulose can be broken up by a process of bacterial fermentation; it absorbs some of the final products of digestion and it returns water to the blood. In man it serves as a reservoir in which waste can be held until such time as it can conveniently be voided, and it serves as an excretory organ for certain substances such as the salts of the heavy metals.

In man, the contents of the colon increase in consistency as they advance from the cecum to the rectum. Especially in constipated persons, one can see with the roentgen ray that already in the hepatic flexure the feces have begun to form into rounded masses. Some of this early drying out may be due, however, to the presence of the barium. From this point onward there seems to be no churning of the material and, as is pointed out in Chapter XXII, the rounded masses are pushed into the rectum like cars on a track.

Movements of the Colon. In man, the material coming from the ileum seems to be pushed ahead through the cecum and ascending colon in much the same way that a barium enema is pushed from the anus to the cecum, without the help of any peristaltic waves that can be made out on the fluoroscopic screen. At various times during the day, there appear what are called mass movements. These were decribed by Hurst in 1907 (p. 423) and in 1908 (p. 9), by Holzknecht in 1909, by Barclay in 1912, and later by Hurst and Newton, Case (1915), and others. I have seen them several times, generally in persons with a tendency to diarrhea. The haustrations in the middle of the transverse colon disappear and the fecal material runs together into a sausagelike bolus some 15 cm. long. A contraction then

appears, and in the next four or five seconds pushes the mass over into the descending colon or rectosigmoid. In animals, and probably in man, these mass movements in the colon are often secondary to a rush wave in the small bowel, and they not infrequently result in a call to defecation.

FIG. 67. Diagrammatic representations of serial roentgenograms showing a mass movement in the colon. (*From Hurst and Newton.*)

A man with an incompetent anus which allowed every mass movement to result in defecation told me that he usually had a call as soon as he got out of bed in the morning, another when he began to eat breakfast, and one or two more following that meal. After that, in order to save himself trouble, he had to avoid the sight, smell, or even thought of food, so in walking down the street he was careful not to pass in front of restaurants. A few of his friends, knowing his weakness, would sometimes amuse themselves by discussing before him the relative merits of Hungarian goulash and beefsteak and onions. It seems, therefore, that as Cannon suspected, a psychic stimulant not only makes us "dribble at de mouf" (Br'er Rabbit), but must cause the stomach and bowel to gird themselves for the handling of the feast.

In the cat the descending movements may be very powerful; the whole colon shortens and becomes blanched; and I have seen a hemostat, clamped on the rectum, twisted in two. Such powerful contractions are produced when the colon is filled with soapy water and then tied off a little above the anus.

Reverse Peristalsis in the Colon. In addition to the downward peristalsis in the colon there are reverse waves which in some animals run over the proximal third or half of the tube. (Sanders, Jacobj, 1890, p. 127; Cannon, 1902, p. 265 1911[a], p. 152.) Ordinarily they are rather shallow, and I have

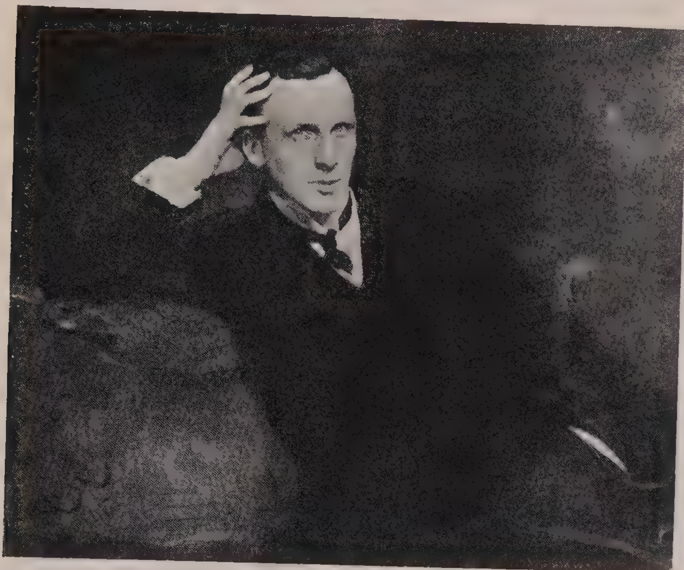

FIG. 68. Arthur F. Hurst.

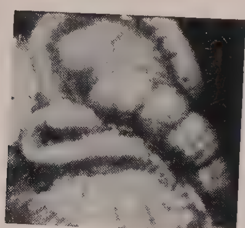

FIG. 69. Reverse peristalsis in the colon of a cat.

never seen them pushing material forcibly against the ileocecal sphincter except in those cases in which I had filled the colon with liquid and then tied off the rectum. Lenz (1923) however, using abdominal windows, has seen them coursing

quite deeply over the colons of cats, particularly when the animals had been purged.

There are about 6 of these waves a minute; they run for a while and then disappear. Their behavior can be changed by the giving of purgatives and enemas. They have been seen in the rat and guinea pig, and to some extent in the rabbit, hedgehog and ferret (Elliott and Barclay-Smith, and

Fig. 70. James T. Case.

Zondek). I have been studying rabbits for years but do not remember ever having seen reverse peristalsis in the colon. Case (1914[a] and 1915[a] p. 687) and others have seen it in man, but it must be very unusual, because most observers have looked for it in vain. Stierlin and Fritzsche saw reverse transport in the right side of the colon of baboons, but no reverse waves.

Kästle and Bruegel took many plates at intervals of from one to five minutes and found very little movement in the

haustra. We do not know what these haustra are for in man, but there are some interesting observations by Rutherford (p. 30) on a patient with a cecal fistula which indicate that a haustrum grasps a small mass of moist feces, envelopes it, grips it until it is dry and then pushes it back into the lumen of the bowel.

There is some evidence that when defecation is postponed, the fecal material can pass back into the descending or even the transverse colon (Schwartz, Bergmann, and personal observations), but it is not known just how or when this takes place. According to Hurst, it accounts for the emptiness of the rectum in many persons, but I doubt the force of that argument because, in my experience, the rectum is often full of feces. It is generally found that way during pelvic examinations in women, and one can rarely see much with the proctoscope until the patient has been purged or given an enema.

THE SLUGGISHNESS OF THE COLON. One of the characteristic features about the muscle of the colon is that it is sluggish; and as one would expect, excised bits of muscle generally have a slow rate of contraction. They show also pronounced tonus waves. Plant and Miller put balloons into the colons of unanesthetized dogs and found from 7 to 14 waves per minute, superimposed on tonus waves which came from 7 to 10 times in ten minutes.

Many observers have noted that the colon, with the exception of the rectum, is tolerant of distention. In patients with an artificial anus I have put balloons into the colon, and on blowing them up, have been able to excite only two or three contractions, whereas with similar fistulas into the jejunum, I have obtained records of almost continuous activity. Apparently, then, the muscular and nervous apparatus of the colon is designed, as it should be, for holding material quietly for hours at a time. The descending colon and sigmoid flexure are probably more sensitive because they are often empty when the rest of the colon is full of barium-containing feces. According to Roith (1909) these regions are found empty in 70 per cent of necropsies.

The sigmoid appears to have a high degree of irritability because in cases of volvulus the symptoms are often violent and much like those that are seen with high small-intestinal obstruction.

In the rabbit and probably in other Herbivora with ovulated feces, the neuromuscular mechanism of the colon appears to be highly specialized so that the little balls can be formed and then passed onward like beads on a string. Even when this part of the bowel contains only air or water, two deep contractions tend always to travel caudad with a short relaxed section between them. Intussusception seems to be part of the normal process by which the little balls are formed and then passed onward. Even when the lower colon of the rabbit is removed from the body and kept in Ringer's solution, it continues to grip the fecal masses so firmly that it is hard to move them without bruising or tearing the wall.

In man, also, the colon holds the fecal masses so firmly that it is doubtful if one could ever move them forward by massaging along the course of the bowel. Even with thin persons, placed behind a fluoroscopic screen so that I could see what I was doing, I have never been able to accomplish anything along this line. I do not wish to deny the statements of those who say that massage of the abdomen is sometimes followed by a bowel movement, but I feel sure that they are mistaken in assuming that they pushed the feces caudad.

The Position of the Colon. Gravity probably plays little if any part in the progress of material through the colon, and gastroenterologists are paying less and less attention to the position of the tube in the abdomen. Besides, as was found by Moody, Van Nuys, and Chamberlain in their study of 600 normal students, the colon is so frequently situated in the pelvis that that must now be regarded as its normal position. Another extensive study showing the great variability of the colon has been made by Davis. Some physicians feel that the marked kink at the splenic flexure and the usual high position of that part of the bowel must constitute a hindrance to peristalsis, but there is little evidence in favor of such a view, and I have seen

mass movements traversing that region without a sign of difficulty.

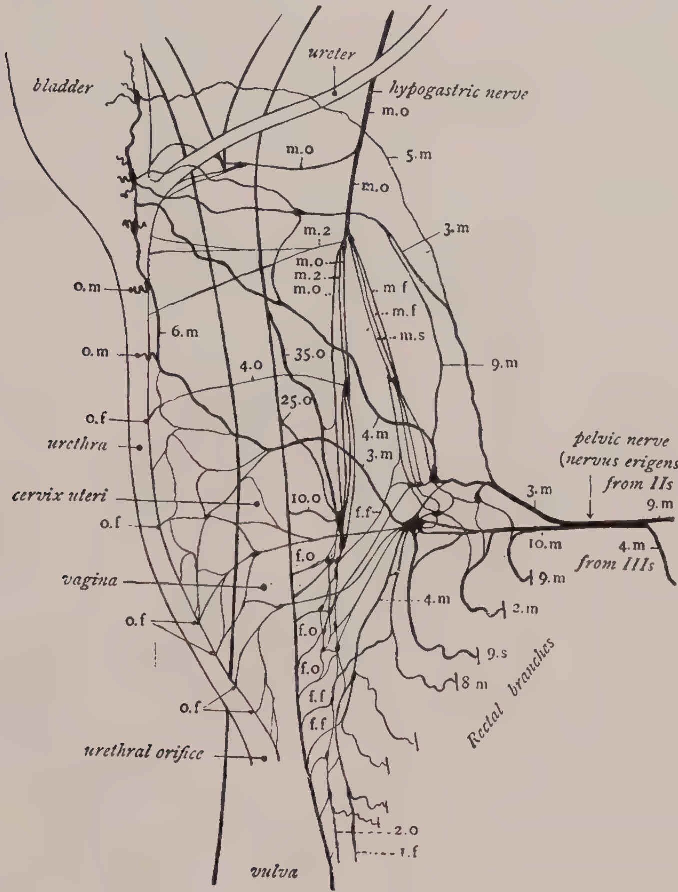

FIG. 71. Left pelvic plexus of cat. The three sacral nerves and the 1st coccygeal nerve were cut distal to the spinal ganglia and eleven days allowed for degeneration. The numbers placed opposite each strand show the number of normal and of degenerated fibers found; the number of normals is given first. For further details see the original article. (*From Langley and Anderson.*)

NERVE SUPPLY OF THE COLON. Before attempting to discuss the abnormalities of defecation, seen particularly

with destructive lesions of the cord, I think it best to review the nerve supply of the colon, the rectum and the anal sphincters. In the first place, according to W. H. Gaskell (1916, p. 52) Bayliss and Starling (1900), Klee, and Elliott and Barclay-Smith, the vagus does not supply any part of the large intestine, and the work of Elliott (1904) indicates that it does not reach even to the ileocolic sphincter. However, some doubt has since been cast on this view (Boehm and Pal), and it may be that different results would have

Fig. 72. J. N. Langley.

been secured with balloons recording in unanesthetized animals. The main supply comes from the anterior roots of the sacral nerves through connector neurones which join together to form on each side the nervus erigens, better termed the pelvic nerve. This connects with those plexuses in the wall of the bladder and rectum which are generally called hypogastric but which, as Langley pointed out, are so much more intimately connected with the pelvic nerve that they should be called the pelvic plexuses.

This system of pelvic nerves and ganglia corresponds to that of the vagus in the wall of the small intestine. Corresponding to the sympathetic supply of the small bowel, there

are the hypogastric nerves which run from the inferior mesenteric ganglia to connect with the pelvic plexuses. The inferior mesenteric ganglia are connected to the anterior roots of the lower lumbar cord by a number of fibers which by some are called the inferior splanchnics, but which, to avoid confusion, should better be called the spinal rami of the inferior mesenteric ganglia. The effect of stimulation of these nerves is inhibitory to the colon except at the internal sphincter of the anus. That bit of muscle responds with contraction just as it does when epinephrin is applied. It resembles, therefore, the pylorus and the ileocecal sphincter. According to Bayliss and Starling (1900) the true splanchnics have no effect on any part of the colon.

Some of the sensory nerves in the colon appear to run with the sympathetic fibers much as they do in the upper abdomen, and many others reach the cord through the pelvic nerve, one third of which is made up of afferent fibers (Langley and Anderson, 1896[a]). There are anatomic and physiologic differences, however, not only in animals of different species but in the male and female of the same species. Thus, as Langley and Anderson (1895) pointed out, the contraction of the internal anal sphincter after stimulation of the hypogastrics is marked in the cat but slight in the rabbit.

In the cat the tone of the internal sphincter is markedly diminished after section of the hypogastrics and still more after extirpation of the inferior mesenteric ganglia. Stimulation of the pelvic nerves produces a contraction of the longitudinal muscle of the lower colon which leads to defecation; it leads also to a contraction of the external sphincter and of the other striated muscles about the anus. The internal sphincter may either contract or dilate but the effects in the cat are weaker than those in the rabbit.

In the rabbit, stimulation of the pelvic nerves causes contraction of both muscle coats of the lower colon so that the bowel is pulled toward the anus. Atropin interferes with the contraction of only the longitudinal coat. Stimulation of the pelvic nerves relaxes the internal sphincter and causes defecation unless there is too much contraction of the external sphincter. Slight dilatation of the internal sphincter

can be produced by weak stimulation of the hypogastrics. Stimulation of the nerves running to the colon along the inferior mesenteric artery usually causes marked blanching of the bowel.

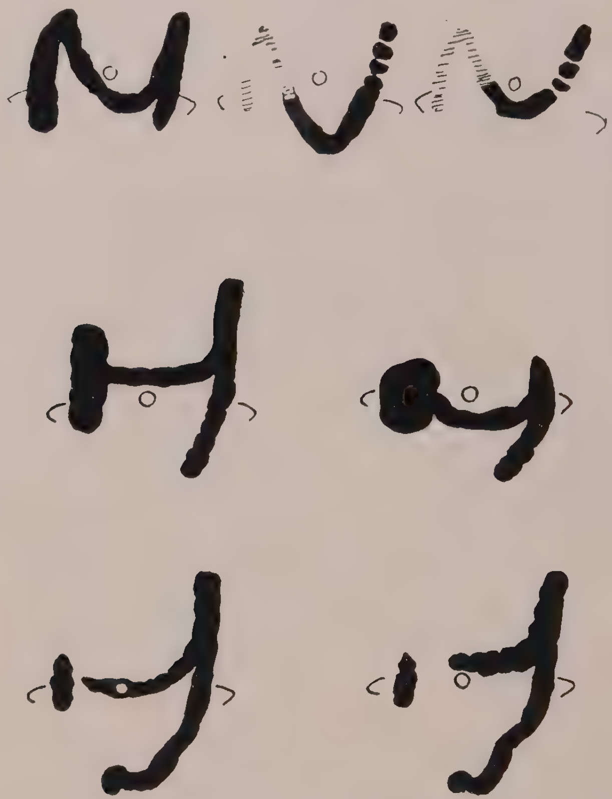

FIG. 73. Diagrammatic copies of roentgenograms, the first three illustrating the condition of the colon before and after defecation; the lower group showing the bismuth shadow before, during, and after the act. (*From Hurst*, 1909.)

DEFECATION. As Hatcher has pointed out, there are many points in common between vomiting and defecation, and both are brought about by the combined and coordinated efforts of voluntary and involuntary muscles. Just as a dog assumes a peculiar position in vomiting, so also he assumes

one for defecation. Strange to say, there seems to be a center in the medulla for defecation close to the one for vomiting, and Hatcher has found that even minute traces of certain drugs applied at this spot will produce diarrhea. (See Chap. XXIII.)

In man the movements of fecal masses in the colon during defecation have been observed by Hurst (1907, and 1909, p. 30) who gave the subject a bismuth meal and studied him later under the roentgenoscope. First there was a marked depression of the diaphragm which forced the bowel downward and caused the ascending colon to assume an almost globular form; then peristaltic contractions in the cecum and ascending colon forced some of the feces over into the transverse colon, and about the same time the descending and pelvic colon emptied themselves.

Hurst's impression from studying a number of subjects before and after defecation was that the whole colon takes part in the act and that material moves from the right half into the middle to take the place of that which has been evacuated. In most of his subjects all of the bowel distal to the splenic flexure was emptied during defecation, but in some, even the rectum was not entirely evacuated. In one person he could see that a strong desire to empty the bowel had been stimulated by the descent of fecal material into the rectum (Hurst and Newton).

The fecal masses are forced through the relaxed anal canal by the combined efforts of the rectal and abdominal muscles. Toward the end of the act the levator ani helps by pulling the anal canal upward over the mass. In the horse and sometimes in man there is a tendency on the part of the rectum to empty itself completely by a process of prolapse and eversion of the mucous membrane.

As Elliott (1907, p. 440) has pointed out, one of the most interesting bits of striated muscle in the body is that which makes up the external sphincter, because when separated from its nerve supply it does not degenerate; it retains its responsiveness to the faradic current, and it even regains much of the tone that it loses immediately after the operation. According to Frankl-Hochwart and Fröhlich, it has a

long latent period and a long plateau of contraction, and as one would then expect, it is easily tetanized. Furthermore, if one stimulates the peripheral end of one of the nerves running to the sphincter, the muscle will respond with two contractions, one immediately after the other (Arloing and Chantre). This resemblance to the behavior of smooth muscle can be seen also in the fact that it will contract rhythmically after transection of the cord (Goltz and Frensberg) and sometimes after cutting some of the nerves. It seems also to be fairly immune to the action of curare (Cannon, 1911[a], p. 207, and Frankl-Hochwart and Fröhlich).

Frankl-Hochwart and Fröhlich point out that there are several muscles that can be called into play to restrain defecation: first, the internal sphincter, then the external sphincter, the levator ani, and finally the other voluntary muscles about the perineum. The experience of surgeons has been that cutting the external sphincter produces less disturbance than cutting the internal one, but there are exceptions to the rule. Experiments on dogs have shown that the two sphincters are about equally effective in keeping the anus closed.

Centers in Cord and Brain. In man the most important nervous centers for the sphincters are apparently in the third and fourth sacral segments of the cord, but some tonic influences seem to come also from the brain. Several workers (Luciani, p. 373, and Hatcher and Weiss, 1923) have found places in the brain where stimulation will affect the tone of the sphincters, and it may be that such centers develop during infancy when the child learns to keep himself clean. It may be also that they have something to do with the voluntary inception and restraint of defecation, and with the incontinence that comes with fright, with old age, epilepsy and other diseases in which the brain is damaged. Köhler, in his book on the "Mentality of Apes" remarks on the fact that a glimpse of a toy animal that frightened his chimpanzees purged them promptly and thoroughly.

Hatcher and Weiss (1923) found a place in the floor of the fourth ventricle, close to the vomiting center, where the application of .016 mgm. of picrotoxin would almost immediately produce diarrhea. In one animal one-sixteenth of

this dose caused the animal to defecate. Other substances which acted on this center were nicotin, quinin, cocain, heroin, aconitrin, veratrin, emetin, strychnin and sodium salicylate. Urination and hiccup were produced sometimes when pilocarpin was painted on the floor of the fourth ventricle. That dilation of the anal sphincter will markedly influence the respiratory center has long been known to proctologists and anesthetists.

Autonomy of the Rectum. Frankl-Hochwart and Fröhlich made extensive studies of the effects on the sphincters of many procedures, such as cutting various nerves and giving drugs, and came to the conclusion that the rectum possesses a high degree of automaticity. This was to be suspected from the fact that with lesions of the cord, rectal incontinence and failure of defecation are much less frequently seen than are the corresponding disturbances of bladder function. Part of this difference may be due to the difference in the consistency of the materials to be held back by the sphincters of the two receptacles, but it is not all due to that, as shown by the fact that in the presence of a diseased cord and an incompetent vesical sphincter, rectal continence will sometimes be maintained even at those times when the patient is suffering from diarrhea.

These observations fit in with those of Goltz and Ewald who succeeded in keeping dogs alive for years with the cord either transected at various levels or destroyed from the seventh cervical segment downward. Immediately after the destruction of the lumbar and sacral cord the anus was relaxed and gaping, and in some animals for several days there was diarrhea, but gradually this cleared up; the digestive processes and defecation returned to normal; there were one or two movements a day, and the rectum each time was well emptied. Even the dogs with only a cervical cord seemed to digest well so long as they were fed carefully. The condition of the animals was better after transections than after excisions because when the lower end of the cord was left it soon regained much of its ability to mediate reflexes.

The most severe disturbances in defecation seem to be produced by destruction of the afferent nerves from the anal

region because when an animal or a man cannot take cognizance of fecal material in the rectum, there is nothing to start the chain of reflexes that bring about defecation.

Merzbacher cut the sensory roots of the three sacral nerves in the dog and produced anesthesia of the anus and part of the rectum. At first the anus gaped but after three weeks it regained enough of its tone to stay closed. These animals were badly off because there was no call to defecation, and feces stagnated and dried out. Finally enough material would accumulate in the colon so that a part of the plug in the lower end could be pushed out; the rectum itself remained passive, and the dog made no attempt to defecate. It appeared, therefore, that the stimuli that start the reflex activity of back, tail, pelvis, abdominal muscles, and levator ani come only from the lower rectum or from the sphincter. In this connection it is interesting to note that Goltz' dog that was kept alive for some time after decerebration assumed the usual position during defecation, as did also dogs with the cord transected.

Somewhat similar studies have been made in dogs by Fröhlich and Meyer who cut the sensory roots of all the nerves below and including the fourth lumbar and found the colon still sensitive to pain. Sensation was present also after the destruction of both major splanchnic and both hypogastric nerves, but it disappeared finally when they cut the sensory roots of the last three dorsal and the first four lumbar nerves and destroyed the cord below that.

Balint and Benedict in studying persons with destructive lesions of the lower sacral roots found complete paralysis of the external sphincter of the anus, anesthesia of the rectal mucosa, absence of the reflex from the anal folds, and relaxation of the anal ring. In spite of this relaxation the subjects were generally constipated because they could not feel the presence of feces until a large mass had accumulated. In some, defecation was uncontrolled, but in most cases the patient could wait until he reached the toilet, and even in the one case in which there was a diarrhea (from tuberculosis) the woman never soiled herself.

A somewhat similar study has been made by Stookey who analyzed the behavior of the rectum with tumors in different parts of the cord. Bladder and rectal disturbances occurred in 41 per cent of the cases of intramedullary tumors, in 78 per cent of the extradural, in 80 per cent of the extramedullary, and in 83 per cent of the conal and cauda-equinal. Strange to say, there was no constant relationship between levels in the cord and degrees of sphincteric disturbance; and rectal weakness was seen sometimes even with tumors in the thoracic region. Constipation was present in almost all the cases, but it is such a common complaint generally that it was not easy to say always how much the tumors had to do with it.

Marked sensory changes about the pelvis were present in every case of incontinence of bladder and rectum, but there were 2 cases in which changes were present without affecting the sphincteric control. It seemed clear, however, that rectal functions are disturbed much more by destruction of the sensory than of the motor paths. Some puzzling cases seen by Stookey could be explained only on the assumption that the afferent and efferent visceral impulses travel by separate pathways, one of which has several relays zigzagging from one side of the cord to the other, and the other, only one long neurone running all the way up on one side. The first pathway may thus escape destruction when the other is completely blocked.

CONSTIPATION

A full discussion of the subject of constipation would be beyond the scope of this book, so I shall just mention some of the ways in which the functions of the colon might be disturbed.

Atony of the Muscle. Most writers on constipation have stressed the importance of dividing all cases into two groups: one with atonic and the other with spastic colons. My impression is that this classification is valueless, for I do not remember ever having seen a constipated person with an atonic-looking bowel, and some of my friends with large

practices who have looked for one for me have been unable to find any. That there may still be something in the idea, however, is indicated by the work of Larimore who has gone at the subject more systematically than have most of his predecessors. The difficulty even with his careful measurements is that any two men of experience would probably, in many borderline cases, differ as to what is tonic and what atonic; and furthermore, if he had done his work with barium meals and not with enemas, his atonic colons might all have disappeared.

From my experience with animals, I doubt whether the colonic muscle is ever so weak that it cannot empty the rectum. It often fails to do so, but that must be due to inhibition or to the absence of the proper stimulus.

Against the idea that atony or weakness of the bowel is a common cause of constipation, is the fact that Müller and Hesky were able to remove all the muscle from the colons of dogs without producing much disturbance. Apparently the small intestine was strong enough to force the material onward through the inactive segment.

A Reversal of the Rectal Gradient. There are some reasons for believing that normally the tone of the rectum and sigmoid is higher than that of the colon immediately above (Alvarez and Starkweather, 1918[e], Rost, 1912, p. 992), and such an upward gradient at the end of the colon, like that at the end of the small bowel, might be very helpful in keeping material from packing up against the sphincter except at those times, as after a meal, or after a peristaltic rush, when the pressure from above is great. The existence of such an upward gradient might also explain the fact, already commented on, that when defecation is postponed, the feces are sometimes returned to the upper colon (Schwartz, Drummond, Kästle and Bruegel, and personal observations).

Any increase in the steepness of this gradient, or simply a tightening of the sphincters such as we should expect to see with irritating lesions about the anus might easily produce constipation, and actually this is the way in which the trouble seems sometimes to arise. The physician who does not often pass an anoscope has no idea of the frequency with which

constipated patients present a reddened, irritated, and fissured anal ring, with hemorrhoids and inflamed crypts. Such patients should be referred to a good proctologist for treatment because, with the clearing up of the local inflammation, the constipation is sometimes cured.

In other cases the increase in tone of the anal sphincter is probably but a part of that general increase in the tenseness of all the voluntary muscles that is seen in tired and highly nervous persons, and in still others the source of irritation may perhaps be found in disease of neighboring organs, such as the prostate, uterus and adnexa. It seems to me that such a contracted anal ring might produce constipation by holding the feces back above the point where they can start the chain of reflexes that bring about defecation. The normal anal ring is perhaps a centimeter wide while these diseased and spasmodically contracted ones appear to be all of 2 cm. wide. When a bolus of food reaches a certain point on the back of the tongue, swallowing becomes inevitable; and similarly, when fecal matter reaches a certain point in the anal canal, defecation should become easy. Against this idea that the reflexes fail because feces cannot get down far enough into the anal canal is the fact that in many persons even the presence of a column of feces part way through that canal is not sufficient to bring the colonic muscles to the help of those in the abdominal wall. Constipation in infants is best treated by dilation of the anal sphincter. This can be done with a little cone whittled from a piece of Castile soap.

Hurst has pointed out that there should be a distinction made between true constipation, which perhaps originally implied a slowing of the progress of material through the colon, and what he calls dyschezia, which is an inability properly to empty the rectum. Occasionally I have found it helpful to show patients their roentgenograms so that they might see that most of the barium they had taken twenty-four hours before was in the rectum, from whence it might easily be dislodged with the help of a little water. They would then agree with me that it was foolish to upset with purges ten or more feet of digestive tubing in order to clear out the last eight inches.

Loss of Irritability of the Rectum. It is commonly assumed, and perhaps rightly, that a frequent cause for constipation is a loss of sensitiveness in the rectal mucosa due to the neglect of Nature's calls. Strange to say, however, one meets with cases in which the rectum that is not sensitive enough to respond to the presence of feces with movements of defecation, is sensitive enough to respond with exaggerated sensations of fullness, headache, and "autointoxication."

Lack of Vis a Tergo. In some cases of constipation the trouble is due apparently to a lack of the normal drive through the digestive tract; and this is due to an interruption of the current at some point, usually at the pylorus or at the ileocecal sphincter. This probably accounts for much of the constipation seen with ulcers obstructing the outlet of the stomach and with appendicitis causing spasm of the neighboring sphincter. Furthermore, in cases of severe pyloric obstruction very little food is getting through, and this leaves the colon with almost no residues from which to make feces.

A Thrifty Colon and a Poor Diet. Constipation may develop if the colon is too thrifty in absorbing food residues and water, or if the diet is too poor in roughage or in other substances that stimulate peristalsis.

The Abuse of Purgatives. As is pointed out in Chapter xxii, the main reason why many persons do not get back to normal habits after the use of purgatives is that they do not know that after a thorough cleaning out they must wait two or three days until the colon fills again. It is possible also that the long-continued use of purgatives can, in some cases, so diminish the sensitiveness of the bowel that it must have stronger and stronger stimuli in order to act.

Obstruction, Megacolon, Mucous Colitis. Especially when constipation comes on late in life in a person who has previously been normal, the physician must think of some lesion obstructing the lumen of the bowel: a carcinoma, an inflamed diverticulum, or a fibroid tumor of the uterus. Severe constipation in childhood is often due to a great enlargement of the colon, which in turn is due probably to some developmental defect in the sigmoid region. Mucous

colitis is probably not a true colitis but a hereditary spasmodic affection seen generally in neurotic women with poor ovaries. In persons with a tendency to this condition the colon is doubtless irritable, but in my experience it is not easy to show any actual inflammatory lesion, either at operation or necropsy.

Rational and Permanently Effective Treatment. As everyone knows, the treatment for constipation today is largely palliative, and consists as a rule in making the feces more irritant, chemically or mechanically. Occasionally the removal of a diseased gallbladder or appendix, or a large fibroid, or some hemorrhoids, or the making of a gastro-enterostomy will really free the patient from his dependence on a nightly laxative or a daily dose of bran; but usually our medical efforts are directed toward shifting him or her from one laxative measure to another. It seems to me that if we are ever to attack the problems of constipation intelligently and constructively, we shall first have to secure more information about the innervation of the rectum in man, about the ways in which the reflexes of defecation are excited, and about the paths along which tonic influences come to close the sphincters too tightly.

For years I have thought of the possibility of cutting perhaps the hypogastric nerves so as to relax the internal sphincter; and now Dr. Royle tells me that Wade and he have been getting good results in some cases in which they have cut the lumbar sympathetic fibers on the left side. They have obtained relaxation of the lower bowel sufficient even to relieve some children with Hirschprung's disease. This work is very suggestive and it may easily be that out of it will come a radical cure for at least one type of obstinate constipation. Needless to say, possible unpleasant by-effects of such resections must be watched for, and the operation should be done only when there is great need for it and when the patient understands the risks that he is assuming. One difficulty that I fear is that even if operations are devised for the immediate cure of constipation, the bowel will, after a time, compensate in some way and return to its old habits; we know that it often does that after colectomies and ileo-

sigmoidostomies. First there is diarrhea, then normal movements, and finally, constipation again.

THE SENSITIVENESS OF THE RECTUM TO PRESSURE. One of the peculiar things about the rectum is its sensitiveness to slight increases in pressure. Zimmermann found that changes of from 2 to 3 mm. of mercury could be perceived by his subjects, and a rise of from 20 to 60 mm. caused distress. As I have shown elsewhere (Alvarez, 1924[b]) the sensations produced by such distention are those that are commonly ascribed to the presence of toxins reabsorbed from the colon: mental haziness, dopiness, malaise, and headache. That they are not due to such absorption can be seen from the fact that they can be produced by stuffing the rectum with cotton, and that they disappear within a few seconds or minutes after defecation. If they were due to toxins, relief would not come until next day when sufficient excretion had taken place to lower the concentration of poison in the blood. To use a homely simile, one does not sober a drunken man by taking his flask of whiskey away from him.

According to Pearcy and Van Liere, distention of the rectum of the dog produces salivation, nausea, and protracted vomiting; the animal's abdominal wall is rigid, it walks around in a peculiar stiff-legged way, it is miserable, and if the pressure has been strongly applied, it is several hours in recovering. They confirm Donaldson's finding that with such distention of the rectum there is sometimes a definite rise in blood pressure. This rise occurs also in man, and just as in the dog, it disappears as soon as the distending body is removed. In man, distention of the rectum with any unabsorbable substance can produce nausea, loss of appetite, flushing of the skin, sweating, abdominal discomfort, depression, restlessness and mental haziness (Alvarez, Donaldson, and Fröhlich and Meyer).

CHAPTER XXI

THE MECHANICS OF THE GALLBLADDER

Very little was known about the gallbladder and its functions until a few years ago when a number of circumstances conspired to bring the subject into the forefront of discussion. First, physicians rather suddenly awoke to the realization that cholecystitis is one of the commonest diseases with which they have to deal, and that they had been failing to

FIG. 74. Evarts A. Graham.

diagnose correctly a large proportion of the cases. Second, there appeared Lyon with certain theories and claims that called loudly for either proof or refutation. Third, there came Graham and Cole with their new and splendid means of approach to the problems of diagnosis; and fourth, there came Boyden with his demonstration of the possibility of emptying the gallbladder with the help of egg-yolk and cream. As a result, a flood of light has recently been thrown on what had formerly been a rather neglected area of the body, and

not a month now passes that important contributions to the subject do not appear.

Embryology. It may be helpful for the student to remember that the gallbladder arises from the same group of cells which give origin to the liver, the duodenum, the pylorus, and the pancreas. It makes it easier to see why all except the pancreas are supplied by one branch of the vagus nerve (M'Crea), and why they are all more or less related in their functions and their susceptibilities to disease.

Fig. 75. Warren H. Cole.

The early appearance of the gallbladder in embryonic life and its presence in many of the lower vertebrates suggest that it must be an important organ, and yet, in a number of the higher animals it is strangely absent. In some, like the pigeon, it develops in early life and later disappears. The fact that it can be removed with impunity in man and in animals shows, again, that the body can easily dispense with it.

Anatomy. In connection with the physiologic studies to be taken up later, it is interesting to note that the muscular coat is thin and that it contains only one layer of fibers which interlace in every direction. The connective-tissue layer under the serosa is interesting as, according to Boyden (1925),

it is nearly three times as thick as the corresponding layer, mainly submucous, in the intestine of the same animal. There would seem to be some reason for this, as well as for the fact that this coat is rich in elastic tissue. When normally distended with bile, the thickness of the wall of the gallbladder in the cat becomes reduced to at least one-fifteenth of what it was when contracted (Boyden, 1925).

Noteworthy also is the fact emphasized by Graham, that the cystic vein empties into the portal system, so that the

FIG. 76. Frank C. Mann.

blood from the gallbladder has to pass through the liver on its way to the heart. The surgeon will be interested in the great variability in the origin and course of the cystic artery in man (Brewer), and the pathologist will be interested in the richness of the lymphatic supply (Sudler). An interesting review of the embryology and anatomy of the gallbladder has been given by Sweet.

The valves of Heister are of interest if only because no one knows exactly what they are for. They have been studied carefully by Mentzer, who found them absent

in only 8 out of 338 normal gallbladders examined at necropsy. From their appearance he could not see how they could, in health, produce much hindrance to the passage of moderately viscid liquids in either direction. In the diseased gallbladder they probably do produce some obstruction, especially when they become incrusted with inspissated bile and tiny gallstones. The difficulty which the surgeon sometimes finds in expressing the bile from the gallbladder is not necessarily due to the presence of these valves, for the

FIG. 77. Edward A. Boyden.

same difficulty is experienced in the many animals that have no such structure.

The musculature of the common duct has been studied carefully by Hendrickson, Burden, and Matsuno, and by Belou, who has written a monograph on the structure of the biliary passages. The sphincter at the papilla was apparently first described by the American anatomist, Gage, and Boyden thinks that if a personal name is to be attached to this structure, it should be called the sphincter of Gage because his description appeared eight years before that of Oddi. Although there is something in favor of that view, the scientific world probably does right in giving most credit to the man who,

like Oddi, keeps hammering at his subject until most well-informed men know about it. The man who would discover a cure for, let us say, tuberculosis, who would report it in a small, out-of-the-way journal, and then let it be forgotten, would deserve, instead of praise, a jail sentence.

Among others who have studied the sphincter are Hendrickson, Helly, Baldwin, and Mann and his associates. All agree that there are extra fibers surrounding the common duct where it pierces the duodenal wall, but it is not so clear whether these fibers should be dignified with the name of a separate sphincter, except perhaps in the guinea pig, where, according to Mann, there is a definite ring of muscle around the duct a little above the point where it enters the wall of the bowel. Burget, and Copher and Kodama have commented particularly on the obliqueness with which the common duct passes through the wall of the duodenum in some animals. In the dog it runs for from 2 to 4 cm. through intestinal muscle fibers which at times must tend to press on it and close it off.

Comparative Anatomy. This subject which has been studied carefully by Macalister, Mann, Mentzer, Mann, Brimhall and Foster, and others is of great interest if only because it offers an approach to the understanding of the functions of the organ. One is led to wonder if there is anything peculiar about the diet of the animals that have no gallbladder, and if there is any way in which they make up for their deficiency. Actually, many men have tried to find some correlation between the absence of a gallbladder and the type of diet used by the particular animal, but so far without success. Animals like the cow, sheep, and goat which live on practically the same type of food have every variety of gallbladder and duct arrangement, while the horse and some of the deer that graze with them do not have gallbladders. Still more striking is the fact that some mice have gallbladders while the rat, which is closely related in every way, has none.

Furthermore, there is no relation between the nature of the diet and the distance between the papilla and the pylorus; no logical explanation for the fact that in some species the

mouths of the common and the pancreatic ducts are together while in others they are separated, and no constant difference between the structure of the sphincter of Oddi in the animals that have a gallbladder and those that have none.

THE FILLING OF THE GALLBLADDER. In considering the physiology of the gallbladder, one of the first questions presented is: How does it become filled with bile? According to McMaster and Elman, when a period of digestion is over, the tone of the sphincter of Oddi rises, the pressure in the ducts increases, and as soon as it reaches 70 mm. (of bile), bile can begin to flow into the gallbladder. During the progress of digestion the sphincter relaxes, and the pressure in the ducts cannot rise over 100 or 120 mm. of bile because at that point the ducts discharge into the duodenum.

The secretory pressure of the liver has been investigated, mainly in anesthetized animals, by Herring and Simpson, Mitchell and Stifel, Mann and Foster, and McMaster and Elman, and in different species it has been found to run between 125 and 350 mm. of bile. Mann and Foster studied the secretory pressure of the liver in a few unanesthetized dogs and found it constant, between 320 and 345 mm., which is higher than in the anesthetized animals. Under some experimental conditions it rose as high as 550 mm.

Many investigators have studied also the pressure which the sphincter at the lower end of the common duct will withstand; but unfortunately, most of them have used a technic which involved the use of anesthetics and the cutting of both the common duct and the wall of the duodenum. Under those conditions the sphincters of different animals withstood pressures ranging between 50 and 300 mm. of bile.

Potter and Mann inserted small cannulas into the gallbladder and common duct in dogs, and after the animals recovered, watched the changes of pressure which took place from time to time. The pressure in the gallbladder was always low when the animal was fasting and was seldom more than 100 mm. of bile. It was always increased after the taking of food, and especially after the taking of certain foods such as milk. Milk produced the quickest and greatest rise in pressure, a fact which, incidentally, may have some clinical

interest, since many persons avoid milk because they say it makes them "bilious." There are a number of other ways in which milk might conceivably cause trouble in the digestive tract, but it is quite possible that the production of increased tension in a diseased gallbladder is one of them.

In the experiments of Potter and Mann the maximal pressure in the gallbladder appeared usually about three hours after the animal had eaten, and ranged ordinarily between 200 and 225 mm. of bile. From time to time quite marked differences were observed between the pressures in the gallbladder and the common duct, and these suggest that the bile flows into the vesicle when the pressure gradient is in that direction (McMaster and Elman). It is suggestive that Winkelstein and others have found that the gallbladder does not fill when a cannula has been placed in the papilla. Whitaker slit the sphincter of Oddi and observed filling of the gallbladder, but he waited only two days after the operation; and some of my observations make me think that at that time there must still have been enough irritation around the duodenum and the lower end of the common duct to produce considerable back pressure.

The work of several observers suggests that as some of the bile leaves the gallbladder, more enters. Copher showed this by giving tetraiodophthalein daily to a dog. In spite of the fact that the gallbladder was being drained repeatedly by the passage of food through the duodenum, its shadow maintained a constant density, and we must assume that new bile containing the dye must have been arriving at frequent intervals. Auster and Crohn showed also with phenoltetrachlorphthalein that some of the bile secreted by the liver is discharged directly into the duodenum while another fraction is stored in the gallbladder.

Absorption from the Gallbladder. It has long been known that the bile in the gallbladder is more concentrated than that which comes from the liver. According to Hohlweg, 40 c.c. of bile in the gallbladder represents from 240 to 400 c.c. of bile from the liver. These observations have been confirmed and greatly extended by the work of Rous and McMaster. They devised an ingenious technic by means of

which, in dogs, they could collect bile at the same time from the hepatic ducts and from the gallbladder. By measuring the amounts of bile pigment in the two samples they could estimate the degree of concentration. Harer, Hargis and Van Meter, and Boyd have made similar studies, using dyes to estimate the degree of concentration. These observations have made it clear how it is that so small a reservoir can store so large a fraction of the bile pigments and salts coming from the liver.

Mann, Bollman, and Magath brought out the interesting fact that if the gallbladder is removed and the common duct ligated, jaundice will develop in from three to six hours. If, however, the gallbladder is left, it can take up and store so much of the bile pigment that jaundice will not appear until from thirty-six to forty-eight hours have passed.

This function of concentrating bile is now of great clinical interest because the Graham-Cole test for cholecystitis is based on the assumption that a diseased gallbladder will not concentrate a bromin- or iodin-containing dye that is excreted by the liver, and will therefore not become visible in a roentgenogram. To a certain extent this is true (Bollman, Mann, and DePage), but there are many exceptions, and gallbladders that are definitely diseased sometimes concentrate the dye so efficiently that they show up well in the roentgenogram. Furthermore, studies by Caylor and Bollman are showing that there is no constant relation between the ability of a gallbladder to concentrate bile and its response to the Graham-Cole test. Unfortunately, the value of the test is lessened by the fact that the inflammatory changes in cholecystitis are generally more marked in the outer coats of the gallbladder than in the mucous membrane.

Other Functions of the Gallbladder. It is well known that the mucous membrane of the gallbladder secretes a small amount of viscid alkaline mucus. This probably causes trouble at times by serving as a cement for the formation of gallstones.

There are certain clinical observations which suggest that the gallbladder has some effect on the secretory activity of the mucous membrane of the stomach; that is, achlorhydria

and low acidities are frequently met with in the presence of cholecystitis. Some experimental work has been done on the problem but from Mann's review of the literature, it appears that neither in man nor in the dog does removal of the gallbladder have much effect on the secretion of the stomach. Lichty and Pepper placed sterile pebbles in the gallbladder of dogs, and for months afterward studied the acidity of the stomach without finding any constant change up or down.

There is no doubt that the mucous membrane of the gallbladder has the faculty of excreting substances which reach it by way of the blood stream; this was shown by Mann and his associates, who found that a certain amount of rose bengal injected into the veins of a dog will get into the bile even after the cystic duct has been ligated. It is suggestive, also, that acute cholecystitis was found in some of the soldiers poisoned by war gases (Stenhouse), and in dogs injected intravenously with Dakin's solution (Mann). Mann feels, however, that with the Dakin's solution the primary point of injury is probably in the lymphatics in the wall of the organ.

It was shown also by Meyer, Neilson, and Feusier that the gallbladder shares with the liver and a few other organs of the body in the power of removing bacteria rapidly from the circulating blood. Such bacteria are excreted in large quantities in the bile. This function is of great clinical interest because the gallbladder seems often to get damaged in the process so that it remains either as a focus of infection or as an area of minor resistance which is subject to invasion from time to time by any bacterium that happens to pass that way.

The Emptying of the Gallbladder. The discussion on this subject was started in 1917 when Meltzer, one of the grand old men of physiology, put two hobbies of his together and suggested first, that inasmuch as the sphincter of Gage and Oddi must relax when the gallbladder contracts, if the bile is to be extruded into the duodenum, the activities of these two parts of the biliary tract must be coordinated and under the control of the "law of contrary innervation." Second, if this be true, magnesium sulfate applied to the sphincter might produce relaxation there, and at the same

time, contraction of the gallbladder; and third, magnesium sulfate might be injected into the duodenum for the treatment of jaundice and biliary colic.

This last suggestion was acted on by Lyon, who has since done a great deal of work on the clinical side of the problem. At first he thought that Meltzer had been right in his assumption because on injecting magnesium sulfate through a duodenal tube he could get, first, light bile which he thought had come from the ducts, and later, dark green bile which he thought had come from the gallbladder. These observations were confirmed by workers all over the world but all did not agree as to the interpretation.

First, it was recognized by physiologists that there was little real evidence in favor of Meltzer's idea. He relied for his "hunch" mainly on the work of Doyon, but that observer had used poor technic, and his results were later discredited, particularly by the work of Bainbridge and Dale, and Oddi (1897). Actually, a review of practically everything that has been written on the innervation of the bile tract has left me with the same impression that Carlson (1925) has, namely, that the results of stimulating the nerves to this region are so slight, so transient, and so variable that no one should attempt to build theories about them. Finally, there has come the work of Sosman, Whitaker, and their associates, who have shown in the unanesthetized animal that stimulation of the vagus, either in the neck or below the diaphragm, does not produce changes in the size of the gallbladder. Furthermore, when both vagi have been cut below the diaphragm and all the nerves going to the gallbladder along the blood vessels have apparently been removed, the organ still responds perfectly to the stimulus of fat introduced into the duodenum. It seems pretty clear, therefore, that the emptying of the gallbladder must be under the control more of a chemical than of a nervous mechanism.

The theory on which Lyon started his work began to crumble rapidly when it was discovered that many substances other than magnesium sulfate, placed in the duodenum, would greatly increase the flow of bile and would give the typical color changes which Lyon had described.

As these substances do not act primarily by relaxing the smooth muscle of the sphincter at the papilla, it cannot be argued that by contrary innervation they cause contraction of the gallbladder. Another objection is that the emptying of the gallbladder can be effected when, in dogs with a pylorectomy and gastroenterostomy, these substances are absorbed only from the jejunum (Sosman, Whitaker and Edson), and still more ruinous to the theory is the finding by Berg and Jobling that the common duct can be transplanted (minus the sphincter of Oddi) and not disturb the response of the gallbladder to a fatty meal.

Still another objection to the conclusion drawn from the studies with the Meltzer-Lyon technic is that typical B bile has been obtained by many workers from the duodenum of patients whose gallbladder had either been removed or else closed off from the common duct by disease (Crohn, Reiss and Radin, Einhorn; Dunn and Connel, Bassler, Luckett and Lutz). The work of Silverman and Menville, and Sosman, Whitaker, and Edson with the Graham-Cole technic has shown, however, that there is a moderate decrease in the size of the gallbladder shadow when magnesium sulfate is introduced into the duodenum; and a review of the literature leaves one with the impression that Lyon is right when he assumes that the typical dark green B bile does come, in large part, from the gallbladder.

Finally, after all this demolishing of the theory with which Lyon started, it is interesting to see from recent studies on the relations between the pressures in the gallbladder and the ducts (McMaster and Elman) that Meltzer was probably right in assuming that the contraction of the vesicle is associated with a relaxation of the sphincter of the common duct. It is still doubtful, however, whether the association is due to nervous reflexes, and it is still hard to see why relaxation of the sphincter should cause contraction of the gallbladder; it is like relaxing the biceps and hoping that the triceps will thereby be stimulated.

I think we all have erred in taking it for granted that magnesium sulfate relaxes the muscle in the wall of the bowel. There is no question that it would do so if it were to

come into direct contact with the muscle, but it does not: the mucous membrane is in the way, and we all know that the salts of magnesium cannot get through it; in fact, that is why they act as laxatives. To be sure, McWhorter and others have seen a drop in the resistance of the sphincter when they painted the overlying mucosa with a solution of magnesium sulfate, but they could not be sure of the direct action of the drug on the muscle because a similar relaxing effect could be obtained with other substances which, like fat, are stimulating to the duodenum.

It is an interesting fact that until recently it was a question whether the gallbladder ever really empties. While there were a few who believed that the organ empties completely from time to time like a urinary bladder, Sweet has gone so far as to say that it never empties at all, and that the bile that goes in has to be absorbed and carried away by the lymphatics. At the present time, both of these views can be disposed of. If the first were correct one should expect to find an empty gallbladder fairly frequently at operation or necropsy, but, actually, the organ is generally found somewhat distended. We now know, however, that this does not rule out the existence of some contractility because those patients who are operated on or who die slowly have generally been fasting; were they able to eat, the gallbladder would probably more often be found half empty as it is in animals opened during the stage of digestion of a meal rich in fat (Boyden, 1923, 1925, Sosman, Whitaker and Edson, and Mann). With the ordinary meal, rich in carbohydrate and protein, the size of the gallbladder shadow decreases slowly and by imperceptible stages, but there is no question now that the organ does empty its contents into the duodenum. Some absorption of the biliary solids probably does take place, but as yet no one knows how much. The slowness of the emptying of the gallbladder was shown originally by experiments in which dyes and suspensions of carmin or charcoal were injected into the organ and the animal was sewed up again (Auster and Crohn, Winkelstein, Diamond, Johnson).

Movements of the Gallbladder. The muscle of the gallbladder wall is so thin and so obviously sluggish and unresponsive to stimuli that for some time it has been a question whether it ever contracts. It has been shown, however, that it does undergo small, slow, and irregular contractions with a rate, in the dog, of from 2 to 5 a minute (Doyon, 1893[c], Taylor and Wilson, Chiray and Pavel). Some of the workers have opened the animals and have fastened heart levers to the gallbladder; others have put in balloons, sometimes through permanent fistulas (Okada); others, with their animals under local anesthesia, have brought the organ out of the abdomen (Higgins and Mann); and others have used the Graham-Cole technic.

After it had been shown that the gallbladder empties into the duodenum and that its muscular wall is capable of contraction, the next question was: Is it capable of strong contractions or does it play a more or less passive rôle while the bile follows gradients of pressure in the biliary duct system? Some workers have concluded that the emptying is due simply to a drop in pressure in the common duct following the relaxation of the sphincter of Oddi, while others have laid stress on differences in abdominal pressure due to the respiratory movements (Boyden, Winkelstein and Aschner, and Burget).

Such theories have now been demolished through the work of Higgins and Mann, and Whitaker. The first two took advantage of the fact that in the guinea pig the gallbladder projects beyond the edge of the liver, and under local anesthesia they brought it to the outside of the body and watched it for hours at a time. They showed in this way that the respiratory movements are not at all essential. Incidentally, as Whitaker has pointed out, if the diaphragm did press on the gallbladder it would press equally hard on the common duct and on the duodenum, so that there would be no reason for the bile to change its position. Actually, Higgins and Mann could see the gallbladder of the guinea pig contracting slowly, and forcing bile into the duodenum. These movements were not wavelike; as a rule they were sluggish; but occasionally they were fairly quick, as when the organ

was stuck with a hypodermic needle or distended with a solution of sodium chloride. The one sure stimulus to contraction was the introduction of fatty food into the duodenum. The fact that some of the meal injected into the duodenum sometimes was seen to run up the common duct while the gallbladder was still well filled spoke against the theory that the organ empties simply because the sphincter of Oddi is open. In dogs under local anesthesia and with the hepatic ducts tied off, Higgins and Mann noticed, when fat entered the duodenum, a slight but definite increase in the pressure of bile in the common duct.

Whitaker's paper is also conclusive. He used cats in which the bile was removed from the gallbladder and replaced with iodized oil. The animals were allowed to recover and were then studied with the roentgen ray. After the cat was given a meal of egg-yolk and cream, the gallbladder usually began to empty within from five to twenty minutes. At times movements were seen suggestive of shallow peristalsis. The unsatisfactory nature of many of the older experiments by Freese, Okada, and others was shown by the fact that simple anesthesia, or the opening and closing of the abdomen would delay for hours the emptying of the gallbladder. K. F. Meyer has found also in guinea pigs, that anesthesia stops the secretion of bile by the liver, so that in order to get a good flow he had to use a method similar to that of Higgins and Mann. If the animals are sick, the emptying is slow and feeble, or it may fail entirely. Observations closely duplicating those of Whitaker with lipiodol were made about the same time by Hamrick, one of Mann's students.

That the muscle of the gallbladder is, under normal conditions, barely strong enough to contract against the secretory pressure of the liver was shown by Boyden in some cats which happened to have one of the hepatic ducts emptying into the cystic duct. He tied the cystic duct below the point where the hepatic duct came in, and then stimulated the gallbladder by giving the usual meal of egg-yolk. Changes were seen in the shape of the organ but the contractions were not strong enough to force the oil out. Similarly, Mann has come to the conclusion that the pressure exerted by the

contractions of the gallbladder about equals that produced in the hepatic ducts by the secretory action of the liver.

Whitaker found that the gallbladder would not empty simply because the sphincter of Oddi had been cut, but that in addition food had to be given. This food apparently had

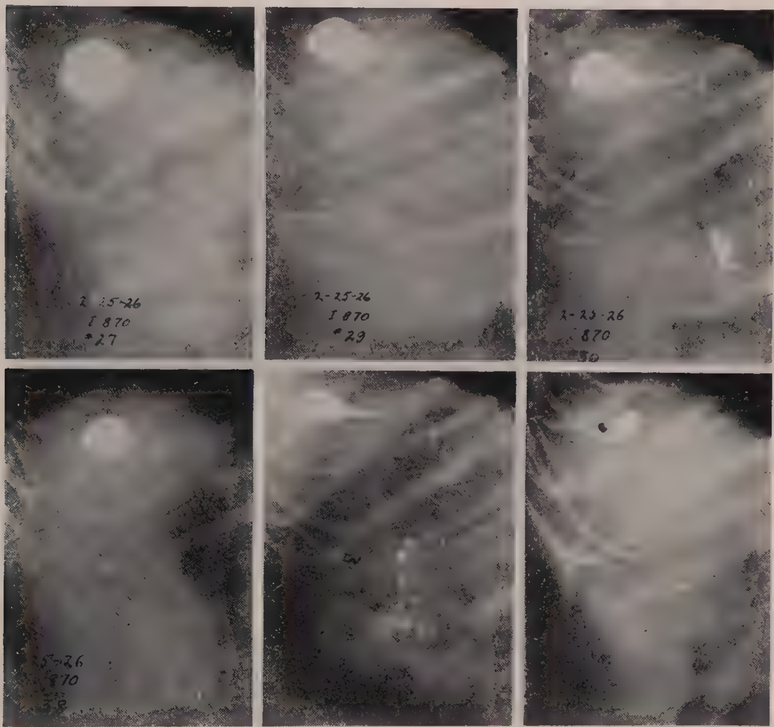

FIG. 78.—Serial roentgenograms of the gallbladder of a dog filled with iodized oil. Read from left to right in the upper row and then from left to right in the lower. Emptying was produced by giving a meal rich in fat. (*From Mann and Hamrick.*)

to be taken into the blood before it could be efficacious; for in two cats with the pylorus tied, the placing of fat in the stomach had no influence on the gallbladder, and it is well established that there is little absorption of any kind from the gastric mucous membrane (Tschekunoff).

Boyden succeeded in emptying the gallbladder by injecting blood taken from another animal during the height of digestion, but he felt doubtful about the significance of the experiment because controls showed that almost as striking results could be obtained by any procedure that alarmed the animal. He thought they were due probably to stimulation of the sympathetics and to a resultant outpouring of epinephrin. He could still get them in a lessened degree after removing the suprarenals, but he found that epinephrin is one of the most powerful stimulants of the muscle in the gallbladder. It seems at the same time to relax the sphincter of the common duct, much as it relaxes the smooth muscle almost everywhere in the wall of the bowel.

The fact that the emptying of the gallbladder was more marked after the injection of blood from digesting animals than after the injection of that from fasting animals, and the fact that the effects could be obtained after denervating the gallbladder, made it seem highly probable that some chemical derived from the food was at work. The tying of the lacteals had no effect on the emptying of the gallbladder, showing that the stimulus does not travel through them. In one animal the portal vein was tied and next day the giving of egg-yolk caused weak contractions in the gallbladder. It is a remarkable fact observed by Whitaker, that if the egg-yolk is given with barium, it has no effect on the gallbladder. It has no effect either, if, as occasionally happens, it passes through the small intestine undigested. To produce marked emptying in man it is necessary to give five raw yolks in half a pint of cream. The measurement of successive roentgenograms shows that the gallbladder empties intermittently, with a varying rate which probably depends on the amounts of effective split-products from food liberated at any one time.

For a while Boyden (1926[a]) hoped that in lecithin he had found the ingredient of egg-yolk that causes the rapid emptying of the gallbladder, but further experiments showed him that he was wrong. In his last paper (1926[b]) he expresses the conviction that the reason egg-yolk works so well is that it leaves the stomach so slowly that it continues to be absorbed and to stimulate the gallbladder for a long time.

If, as in the presence of a barium meal, it is rushed rapidly out of the stomach it does not have any more effect than some other foods. That the egg-yolk does not act primarily on the liver is shown by the fact that the latent period for its effect in stimulating the secretion of bile is about twenty-five minutes while the latent period for its effect in stimulating the gallbladder varies from two to fifteen minutes. Boyden concludes his studies with the statement that the gallbladder is probably under the control partly of the sympathetic nervous system and partly of substances derived from the digestion of fats.

Reach and W. H. Cole observed that distention of the stomach tends to close the sphincter of the common duct. The acidity of the gastric contents seemed also to influence it. According to Sosman, Whitaker and Edson, psychic stimuli, such as the sight, taste, or smell of food, have no effect on the emptying of the gallbladder. Pure olive oil had no definite effect in reducing the size of the gallbladder shadow in man, but its ingestion by dogs was followed by a good response. Sosman and his associates gave a number of drugs to normal students and obtained no constant effect—except perhaps with magnesium sulfate. Sodium bicarbonate by mouth had a slight emptying effect. Vigorous exercise, forced respiration, pressure on the abdomen, and heat and cold applied internally and externally were all without effect. According to Whitaker, the giving of bile salts slows the emptying of the gallbladder and causes it to become distended.

The Meltzer-Lyon Technic. One great objection to the use of this technic diagnostically is the fact that especially in early cases of cholecystitis, the bile and the mucous membrane of the gallbladder show nothing abnormal, and the lymphocytic infiltrations, the inflammatory scars, and the patches of edema are to be found only in the outer coats; that is, in the subserosa and the muscle. Under those circumstances it is hard to see how one could learn much from a study of the bile even if it could be obtained unmixed with other substances. It may be, however, that the bile coming from diseased ducts may contain cells and crystals, the finding of which will have diagnostic values. Those who are inter-

ested in the subject will do well to consult the conservative articles by C. M. Jones, Venables and Knott, Fitz and Aldrich, and Boardman.

Therapeutically the method seems sometimes to give results, but psychic factors are hard to exclude, and when so much of the inflammation is situated deep in the wall of the gallbladder and the ducts, it is hard to see why an increase in the flow of bile should help. It is also hard to see why, if an increase in the flow of bile is beneficial, the giving of food rich in fat should not do more good than instillations of magnesium sulfate. Perhaps we shall find later that it does. Incidentally Soper, and Dunn and Connell claim to have obtained just as much bile from the duodenum when the magnesium sulfate was taken by mouth as when it was injected through a tube. If this is true, there would seem to be no reason, other than financial and psychic, for a physician's spending hours of time on the therapeutic intubation of patients.

The Effect of Cholecystectomy on the Bile Ducts. Years ago Oddi (1888, 1897, p. 81) observed the now well-known dilatation of the bile ducts which follows the removal of the gallbladder. He concluded that after the operation the bile must dribble into the duodenum more or less constantly, and this has since been confirmed by Rost, Klee and Klüpfel, and Judd and Mann. The tonicity of the sphincter is greatly diminished or even abolished for a while after cholecystectomy, but both in man and animals it tends to return, and the discharge of bile into the bowel may finally again become intermittent. In some animals Judd and Mann cut the sphincter when they removed the gallbladder and found that in that case the ducts did not dilate.

Great light has recently been thrown on the cause of these changes through the work of McMaster and Elman (1926); they used unanesthetized dogs with various types of biliary fistula and found that when the gallbladder is removed or shut off, a manometer placed in the common duct will fill to a height of about 320 mm. Ordinarily, in the digesting animal, no such pressure can ever be produced because, as was pointed out earlier in this chapter, the sphincter of Oddi

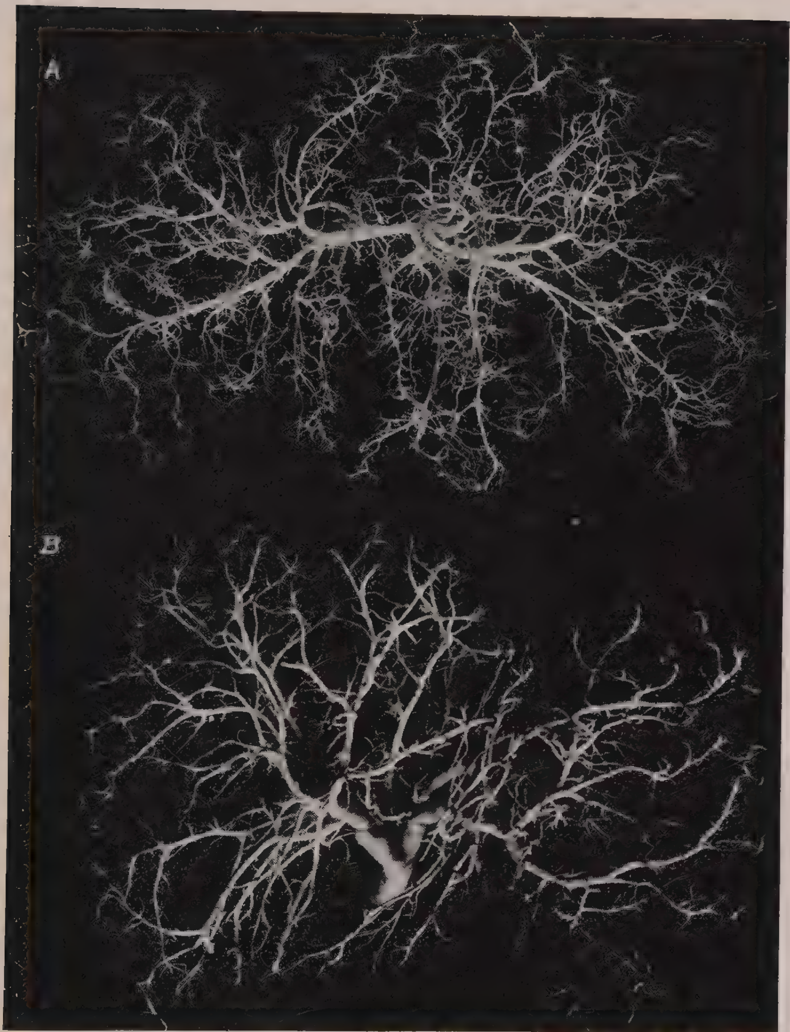

FIG. 79. A, cast of normal bile ducts. B, cast of bile ducts after the gallbladder has filled with stones and ceased to function. (*From Counsellor and McIndoe.*)

will give way when the bile in the manometer reaches a level of from 100 to 120 mm. During the stage of fasting, the sphincter can hold up a column of from 250 to 300 mm., but in the normal animal it is not likely to be subjected to any such strain, because when the pressure reaches about 70 mm., the bile begins to flow into the gallbladder, where it is dehydrated and stored so rapidly that the pressure in the ducts cannot rise over 100 or 150 mm.

It seems to me that this work amply justifies the reluctance of surgeons to remove a gallbladder that is not definitely diseased. To be sure the body can get along without it, but it does seem as if so beautiful a pressure-regulating mechanism should, whenever possible, be conserved.

The Mode of Production of Pain with Gallbladder Disease. It seems commonly to be assumed that the pain of gallstone colic arises in contractions of the common duct or of the gallbladder. I doubt if it can arise in the gallbladder because the muscle there is too sluggish, and besides, patients without a gallbladder sometimes experience severe colic. It is not always due to the presence of stones because not infrequently they cannot be found at subsequent operations (Finkenheim). To be sure, a stone may have passed or the surgeon may have failed to find it, but that cannot be the explanation in all cases, and it is highly improbable in those in which at several successive operations no tendency to stone formation can be seen. In some cases recently studied at the Mayo Clinic, McVicar and Judd could be sure that the colics complained of were not due to the presence of a stone because at operation the common duct was found to have been obliterated by disease or by the trauma incident to a previous cholecystectomy.

As McVicar has pointed out, we can hardly ascribe the colic to dilation of the biliary ducts because that is seen most strikingly in persons who have lost the gallbladder or who have developed a carcinoma of the head of the pancreas, in both of which conditions it generally takes place painlessly. I think we must assume, therefore, that much of the pain of gallbladder disease is produced by cramplike contractions outside the biliary tract, perhaps in

the neighboring stomach and duodenum, or, as Payne and Poulton would have us believe, in the esophagus. Certainly, with the roentgen ray, it can often be seen in these cases that the stomach and bowel are hypertonic, and occasionally there are lasting contractions of the cardia and the pars pylorica of the stomach. It has always been a puzzle to me also why an injection of morphin so commonly puts an end to an attack of gallbladder colic, even when the stone remains wedged somewhere in the ducts. One should expect the pain to return in an hour or two when the effect of the drug wears off, but I do not remember ever having seen that happen. According to Lieb and McWhorter morphin in therapeutic doses has no effect on the gallbladder.

Ivy tells me that he and his associates have recently made some studies on dogs which show that distention of the biliary ducts causes marked distress, disturbance in the respiratory rhythm, salivation, and often vomiting. These symptoms are more marked with distention of the ducts than with distention of the gallbladder. Section of the right splanchnic abolishes the distress and reduces the amount of respiratory inhibition; section of the vagi and left splanchnic stops the salivation and vomiting and reduces respiratory inhibition; section of both vagi and splanchnics abolishes all distress and reflex disturbance. The instillation of 2 per cent procain into the biliary ducts abolished the reflexes, but the drug was so rapidly absorbed that the blockage was probably not due to local anesthesia alone.

SUMMARY

It appears, then, that the gallbladder serves as a reservoir for the bile secreted during the periods when it is not needed. In order to compensate for its small size, it concentrates the fluid which it receives from the liver. It may be that during the process of absorption of water it returns to the liver or to the circulation substances which are of value to the body, but as yet nothing is known about this phase of the problem. It is possible also that the excretory or secretory functions of the gallbladder are of considerable value to the body.

The rapidity with which it concentrates and stores bile enables it to serve as a valuable pressure-relieving chamber for the biliary duct system.

The muscle of the gallbladder is rather weak and sluggish, but it responds sufficiently to substances absorbed during digestion to squeeze out a considerable part of the bile that collects during the interdigestive periods. Associated with this contraction of the gallbladder is a relaxation of the sphincter of Oddi which may be due to nervous reflexes; but most of the evidence seems to be against that view. When digestion ceases, the sphincter of Oddi closes, the pressure in the ducts rises, and the gallbladder fills again.

The student who wishes to go more deeply into the subject than I have done in this chapter should consult the comprehensive article by Mann in *Physiological Reviews*. It is a pleasure here to express my indebtedness to Dr. Mann for having written that article and for looking over the manuscript of this chapter.

CHAPTER XXII

THE RATE OF PROGRESS OF FOOD RESIDUES THROUGH THE DIGESTIVE TRACT

It has generally been assumed by physicians and laymen that the residues from any one meal leave the body within twenty-four or forty-eight hours; and this is the conclusion that one would draw from observing the progress of a barium meal through the bowel of the average person. Unfortunately, it has not been recognized that the addition of a large amount of indigestible material like barium to a small meal of gruel or milk must modify the passage of that meal or its residues through the intestine; the added bulk must act like a large dose of agar or liquid petrolatum, and as one might expect, patients who are being roentgenoscoped for the study of obstinate constipation not infrequently find themselves temporarily relieved.

Obviously, if the normal rate of progress of residues is to be studied, the indicator to be used should have no appreciable bulk; it should mix intimately with the usual food taken by the subject; it should have no influence on the motility of the bowel, and it should lend itself easily to the making of quantitative studies. Actually, the most useful indicator which I have found is a small glass bead with a diameter under 2 mm. Some years ago Dr. Freedlander and I gave to a number of healthy medical students sets of capsules containing fifty of these beads. They mixed intimately with the feces, and so far as we could see had no more influence on intestinal motility than the many berry and fig seeds and bits of fiber that are found so commonly in the stools. Differently colored beads were given on each of three successive days so that three rate-determinations could be made on each student without much extra work. The stools were passed into wide-mouthed fruit jars, and were brought to the laboratory where they were rubbed through a sieve under running water. The beads recovered were counted, and plotted daily as percentages of the whole number taken.

A glance at Figure 80 shows clearly that normal young men with good digestions and daily bowel movements did not, in twenty-four hours, pass 100 per cent or anything like 100 per cent of the beads. There were two who passed about

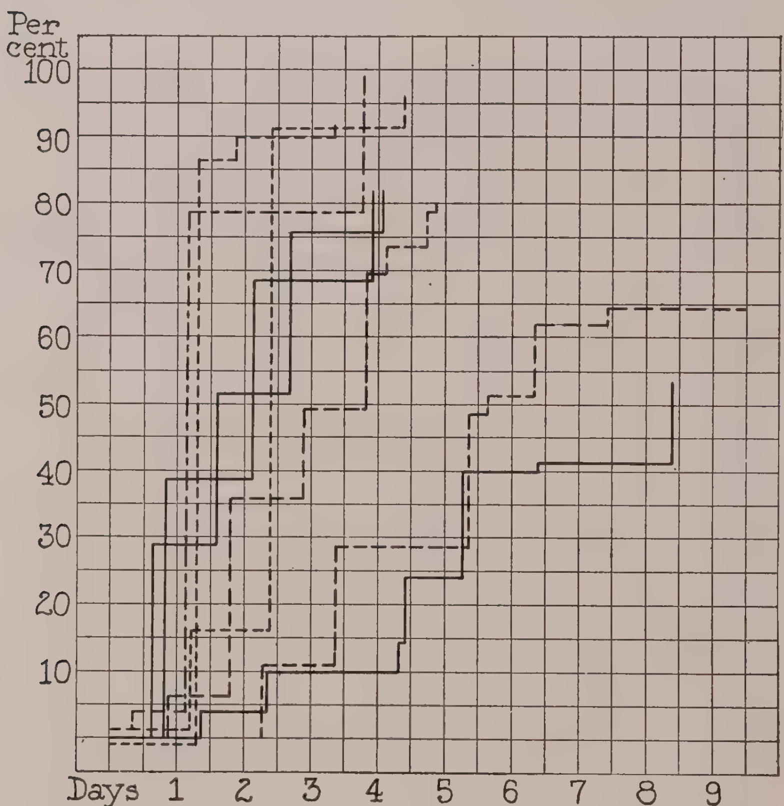

FIG. 80. Shows a wide difference in the rate of passage of beads in eight healthy young men: a rapid rate of 85 per cent in twenty-four hours; an average rate of 75 per cent in four days, and a slow rate of 60 per cent in nine days. The abscissas represent days and the ordinates percentages of the number of beads ingested.

85 per cent in twenty-four hours, but most of them took four days in which to get rid of 75 per cent, and there were some who passed only 50 or 60 per cent in nine days. Most of them passed about 15 per cent on the first day and 50 per

cent more on the second. As Burnett has pointed out from his experience with somewhat similar studies, the subjects with the fast, hitherto supposedly normal, rates had voluminous, soft, frothy, and badly digested stools, so foul that it was

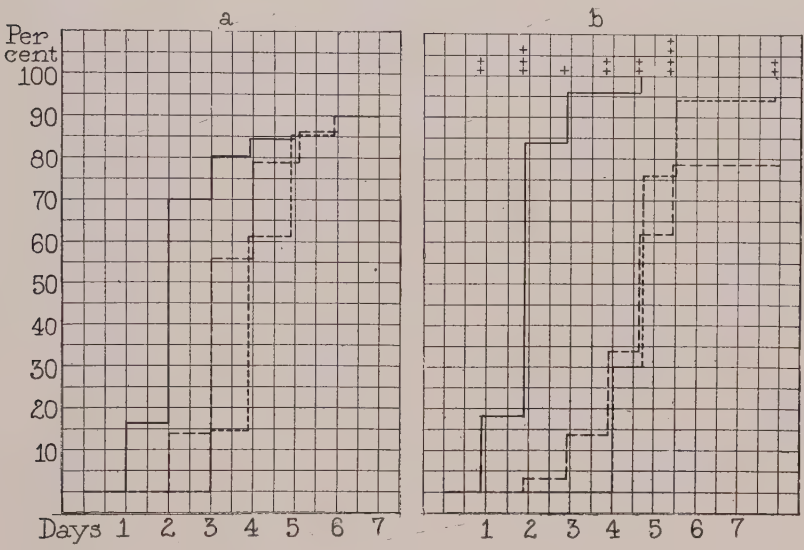

FIG. 81. A shows the most typical rate observed, the figures charted being averages from thirty-seven determinations. The beads given on the second and third day tend to catch up with those given on the first. B shows the faster passage of the first set of beads when 60 gm. of barium is given with them. The number of plus signs indicate the relative sizes of the stools passed. No barium was grossly visible in the stools after the third day.

hard to understand why they were not associated with flatulence and indigestion. Those with the slower rates usually had well-formed, often ovulated stools, which showed evidence of good digestion. As would be expected, some of these subjects confessed to a tendency to constipation.

Figure 81A shows the averages of the figures obtained from the thirty-seven sets of data that seemed to fall most closely in one group, representing what we may perhaps now call the norm. It is an interesting and puzzling fact that the beads given on the second day nearly always came through

a little faster than those of the first day; and those on the third day even faster, so that the third line in the figure often crosses the second and even the first. It would seem as if the first set of beads must get off into the haustra and out of the central current; once there they may perhaps, in some way, keep the later ones from coming in.

The next question is, how can the observations with the beads be reconciled with those with the barium meal? Actually they are not so much in conflict as might at first sight appear. It is well known to roentgenologists that even after the purgation of a patient who has had a barium meal, small masses of the drug will often remain for a week or more to interfere with the interpretation of plates of the kidney region. In order to measure this residue Freedlander and I gave 60 gm. of barium in milk to a number of the students, collected their stools, and recovered the drug quantitatively. We found that usually, by the third day, 75 per cent had come away, and after that there was a slow extrusion lasting over several days.

When barium was given with the first set of beads, its bulkiness, or possibly some split-product, sometimes caused it to act as a laxative. Figure 81B shows that after the passage of a large stool, a day or two may go by during which there is no bowel movement.

Laxatives were given to a few of the subjects shortly after they had taken their beads, with the result that next day nearly all of the beads were passed. Following that, for two days, there were generally no stools. This so-called constipation after purgation has hitherto been supposed to be due to an astringent effect of the drug, but it occurs just as commonly after spontaneous diarrheas, and it seems to me that these experiments with the beads and barium now offer a much simpler explanation. The only trouble with the colon is probably that it has been emptied, and it cannot again contract efficiently until enough material has arrived to distend it. I sometimes liken the colon to a railroad siding on which there are standing three freight cars. Every day a new one arrives and bumps the end one off so as to leave three again. Occasionally one arrives with such force that it

bumps all three off, and then three days have to elapse before the siding again is full enough so that a car arriving at one end can push one out at the other.

The fact that most of the stools are mixtures of food residues—some, such as meat and starch which are easy to digest, and others such as seeds and skins which are hard to digest, indicates that the bowel has little or no ability to pick and choose between those materials which are ready for extrusion and those which might with advantage be held over for further action by the digestive juices.

Food residues are constantly flowing into the cecum where a mixture of new and old must take place. Beyond that region, in men and women whose feces are formed, there is probably little or no mixing. In some fecal columns I have seen such sharp dividing lines between the residues from two different meals, identifiable by the presence of such foods as beans and berries, that I could be sure that after they had left the ascending colon, those residues had traveled the rest of the way to the rectum like cars on a track. This point is of some practical importance because when the end-portion of a formed stool is soft one can be fairly sure that the colon has emptied itself as far back as the hepatic flexure, and that no further evacuation is needed for that day.

From the studies made with the beads it appears that, each day, about one-sixth of the material that arrives from the ileum goes straight on down the colon, and with it, about half of the contents of the cecum.

The essential point for the clinician is that when the colon is well cleaned out by a purge, or by a large bowel movement, no defecation should be expected or demanded for another twenty-four or forty-eight hours. It can come only if the colon is so sensitive that it can respond to the distention brought about by the residues from three meals. Occasionally, of course, a chemical irritant without much bulk is able to produce defecation, but ordinarily a certain amount of distention seems to be the necessary stimulant for colonic emptying.

Furthermore, if very little food is taken, as after an operation or during an illness, or if the colon is unusually long or

large in diameter, or if it is exceedingly thrifty, as it is supposed to be in some Scotchmen, the period of normal waiting may be several days or a week or more. To give purgatives during this time is meddlesome and unjustifiable, except in those cases in which the patient or his relatives become sick with anxiety over the dangers of autointoxication, or in which headaches and distress actually develop. It is questionable, therefore, whether purgatives that produce copious movements should ever be given oftener than two or three times a week. Certainly, one who has been purged and who then wishes to get back to normal must be content to wait a day or two for his first movement.

The Rate of Progress in the Small Intestine. David (1918) has made an extended study of this subject, but unfortunately he used water as a test meal, with 50 gm. of bismuth subcarbonate. The stomach was empty usually in from two and a half to three hours. The cecum began to fill in from two to four hours, and the ileum was empty in from six to eight hours. The results of his observations are here tabulated:

In 124 cases the cecum began to fill	
Before two hours in	36 cases
Between two and three hours in	38 cases
Between three and four hours in	35 cases
After four hours in	15 cases
In 147 cases the ileum was empty	
Before two hours in	5 cases
Between two and three hours in	16 cases
Between three and four hours in	27 cases
Between four and six and a half hours in	83 cases
After six and a half hours in	16 cases

Kantor (1918) who has made similar observations on 161 patients, has found material in the ileum after nine hours in 62 per cent. He thinks ileal stasis is often due to back pressure from an irritable colon.

Another interesting study has been made by Beuttenmüller on a patient with a fistula leading into the cecum next to the sphincter. She found that the use of a dry diet would cut down on the number of hours in which the patient

had to be bothered by the flow of material from the fistula. When large amounts of liquid were drunk a heavy flow began, sometimes within an hour.

Senna leaves, phenolphthalein, and small doses of calomel caused the food to go through the small bowel in from two to two and a half hours, but cascara had little influence on the rate of passage. Solutions of sodium and magnesium sulfate went through in half an hour. With tincture of opium a mixed diet went through in ten and a half hours, and a liquid diet in three hours.

On a mixed diet the material coming from the fistula was mushy; with a liquid diet it was much thinner, and with laxative salts it was watery. With opium the material was thick and somewhat formed. Even small amounts of sodium and magnesium sulfate added to the diet increased the amount of material coming from the fistula. The reaction of the intestinal contents was alkaline, and the odor was not fecal.

Berlatzki (Babkin 1914, p. 386) and Heile showed that the giving of milk increases the rate of progress of food residues through the small bowel so that large amounts will pour out through a fistula made in the terminal ileum. The smallest residues were seen when the animals were fed with meat or pure carbohydrates. It may be that lactose has something to do with the rapid progress of milk through the bowel. Whatever the reason, the observation is important because it can help the surgeon in deciding what diet he should prescribe when he wants to keep the colon at rest. Ordinarily he gives milk, which would seem now to be the last thing he should prescribe.

Lesné, Binet and Paulin have studied the rate of progress through the small intestine of infants at different ages, and Krzywanek has studied the rate through the small intestine of the dog. Schüpbach studied the influence of bile on the motility of the bowel and came to the conclusion that it has an inhibiting effect on the movements of the small intestine and an accelerating effect on those of the colon.

A. Schmidt found that foods rich in cellulose go through the small bowel more rapidly than normal, and this has been

confirmed by Lehman and Gibson, who found while studying a patient with a jejunal fistula, that coarse foods such as the woody fiber of orange pulp or indigestible lumps of doughy bread would greatly intensify all the movements of the bowel. Jellies also tend to hurry the progress of food through the small bowel; some observations that I have made suggest that this is due to the presence of pectins.

CHAPTER XXIII

VOMITING

Vomiting is a rather complicated act which can be started in a number of ways and from many parts of the bowel; hence much of the research work done on it has been directed toward answering such questions as: What part is played by the digestive tract and what by the voluntary muscles of the abdominal wall? What is the importance of the center in the

Fig. 82. Robert A. Hatcher.

brain and through what paths does it receive and dispatch its messages? What are the principal places in the body from which the reflex can be incited? How does the cardia act, and how do the different emetics produce their effects?

As Hatcher points out in his classic review of the subject (1924), the more primitive creatures vomit with the help of the gastric and esophageal muscles alone, but as we come up through the animal kingdom we find many different mecha-

nisms in which the voluntary and involuntary elements are combined in different degrees.

It is an interesting fact, well discussed by Mellinger, and Hatcher and Weiss, that some species of animals vomit, while others, particularly the Herbivora, do not. It has been suggested that they cannot vomit because the stomach lies transversely in the abdomen, because the fundus is large,

FIG. 83. Cary Eggleston.

and the subdiaphragmatic esophagus too long; but the fact that the animals do not even try to retch under the influence of emetics sugests that they lack a well-developed vomiting center.

VOMITING DUE TO THE EFFORTS OF THE DIGESTIVE TRACT ALONE. This can be seen in animals like the starfish which regurgitate the indigestible residues of their food. It has been seen in the frog with its abdomen open, and is there brought about by reverse peristalsis in the stomach.

In the dogfish I once saw powerful reverse waves emptying material from the pars pylorica into the fundus, but they appeared immediately *after* retching movements, and it seemed to me that the food that was vomited must have been ejected by the muscles of the esophagus because the abdomen was wide open, and with the stomach in my hand, I could neither see nor feel contractions at the time when vomiting took place.

I have often seen regurgitation of material from the esophagus in cats in which the abdomen had been so widely opened that not the slightest pressure could have been exerted on the stomach by voluntary muscles; but as Hatcher says, the stomach in such animals does not really empty itself, and we are dealing more with a regurgitation from the esophagus and the fundus of the stomach. Von Bechtereff and Weinberg (1908, p. 259) note also that curarized animals, which cannot vomit on account of the paralysis of the abdominal muscles, will regurgitate if given certain emetics.

Much of what is seen in infants is more regurgitation than vomiting, and is perhaps best described in the words of the child who ran to her mother with the information that the new baby brother was "boiling over." There are many gradations, however, between this type of regurgitation and true vomiting, with varying degrees of assistance on the part of the voluntary muscles.

THE PART PLAYED BY THE VOLUNTARY MUSCLES. Magendie was one of the first to show that vomiting can take place in the absence of the stomach. He substituted for it a pig's bladder. Far more striking, however, is the remarkable experiment of Eggleston and Hatcher who in some dogs, removed the whole digestive tract, from cardia to anus, and showed that typical retching, with some regurgitation from the esophagus, could still take place. Mann tells me also that the dogs from which he has removed every bit of stomach vomit normally if given coarse food, and Rost (1923, p. 67) says that men and women vomit after total gastrectomy. Valenti thought that if the pharynx with its sensitive points were cocainized, vomiting would be impossible, but Magnus (1914) showed that decerebrate animals would vomit after

the whole pharynx, upper esophagus, tongue, soft palate, and larynx were removed. Ordinarily, of course, vomiting is brought about by the combined activity of the digestive tract and abdominal wall, and in this combination, the voluntary muscles play the more essential rôle.

When we consider the length of the esophagus and the viscid nature of much of the food, it becomes obvious that the voluntary muscles of the abdomen must contract powerfully if the stomach is to be emptied. Actually, Moritz (1895[b]) has found that these muscles in man can exert a pressure on the stomach equal to a column of water 3 meters in height.

Gold and Hatcher have found that retching consists of a series of spasmodic and abortive respiratory movements with the glottis closed, during which an inspiratory effort of the chest muscles and diaphragm occurs simultaneously with an expiratory contraction of the abdominal muscles. Although the diaphragm moves downward violently with each retching movement, it remains in a low position throughout the period of vomiting. The more nearly empty the stomach the greater the amount of retching required to empty it entirely. My own observations on vomiting in man agree with those of others in showing that the movements of the diaphragm begin a few moments before those of the abdominal muscles.

It is still a question just how projectile vomiting differs from the more labored type. Perhaps the contractions of the abdominal muscles are better coordinated and more violent, the cardia more widely open, and the contents of the stomach more liquid. It is hard to say also why some persons vomit with ease and others only with great difficulty. In most or perhaps all cases the ability to vomit at will is a gift, but in a few cases it seems to have been acquired during illness and it then may become a bad habit which has to be broken.

Behavior of the Stomach during Vomiting. Most observers have been interested to see how often reverse peristalsis is present during vomiting. Openchowski (1889[b]), one of the early workers on this problem, says he saw, first, a marked activity in the bowel, then a closure of the pylorus, then unrest in the wall of the stomach, beginning in

the pars pylorica and spreading to the lower and middle third of the body, and finally normal peristaltic waves deepening as they approached the pylorus. The fundus seemed to remain quite passive during the stage of vomiting and was distended by material forced back by the deep contractions of the antrum. Similar observations have been made by Cannon (1898[b], p. 373), by me in cats, and by Hesse in dogs.

Cannon's description of what he saw in the stomach of the cat, observed under the fluoroscope after the giving of apomorphin, is so vivid that I give it here in its entirety. "The first change is the total inhibition of the cardiac end of the stomach, which becomes a perfectly flaccid bag. This is followed, when apomorphine has been given, by several deep contractions that sweep from the mid-region of the organ towards the pylorus, each of which stops as a deep ring at the beginning of the vestibule, while a slighter wave continues. Finally, in all cases, a strong contraction at the angular incisure completely divides the gastric cavity into two parts. Although waves continue running over the vestibule, the body of the stomach and the cardiac sac are fully relaxed. Now a simultaneous jerk of the diaphragm and the muscles of the abdominal wall shoots the contents out through the relaxed cardia. As these jerks are repeated, the gastric wall seems to tighten around the remnant of contents. Once during emesis I saw an antiperistaltic constriction start at the pylorus and run back over the vestibule, completely obliterating the cavity, but stopping at the angular incisure. In the process of ridding the gastric mucosa of irritants, therefore, the stomach plays a relatively passive rôle." (1911[a], p. 57.)

A number of observers, among whom may be mentioned Levy-Dorn and Mühlfelder, von Czyhlarz and Selka, Hurst, Groedel, and Alvarez, have observed the stomach of men and women during vomiting and have seen abnormal contractions very similar to those seen in animals. Rarely was there any reverse peristalsis. A striking feature of the picture on the roentgen-ray screen is the jerking upward of the stomach brought about during retching by the contraction of the abdominal muscles.

THE BEHAVIOR OF THE CARDIA AND ESOPHAGUS. In the early studies on vomiting there was much dispute as to the part played by the cardia. Some said that it is forced open and others said that it is relaxed by reflex action. Openchowski came to the conclusion that it is relaxed reflexly by stimuli coming from any one of the numerous parts of the body from which vomiting can be started; and recently many of his views have been confirmed by Carlson, Boyd and Pearcy, and by Hatcher. Some observers report having actually seen the cardia dilate at the onset of an attack of vomiting.

That it must be relaxed actively and not passively is indicated, also, by the fact that the powerful pressure exerted on the full stomach by straining at stool, heavy lifting, or coughing is never sufficient to force food into the mouth. I have often noticed also that in the anesthetized cat or dog with the abdomen open, no amount of manual pressure on the stomach will force air or fluid out into the esophagus. I am fairly certain, however, that this resistance is produced by a valvelike action at the opening in the diaphragm, for it does not seem possible that the weak muscle-ring at the cardia could hold so firmly. Besides, I have felt it relaxed and I have relieved the obstruction by pushing the stomach toward the spine. In this connection it is interesting that some persons cannot strain at stool at those times when they have a feeling that they are going to regurgitate or belch; they have to wait a moment until a little gurgle runs up the esophagus and then the inhibition is removed.

After vagotomy, which paralyzes the esophagus and upsets the mechanism that ordinarily relaxes the cardia, Hatcher and Weiss (1923) saw cats vomit mucus from the esophagus only.

Hesse took serial roentgenograms of the esophagus during vomiting and could see that the cardia remained open. The food was carried back and forth through the tube several times during the act of retching; sometimes most of it was returned to the stomach. This point will be of interest to clinicians who often have cause to wonder how a hysterical girl can vomit so much without losing weight.

Mellinger watched the exposed esophagus of the dog during vomiting and saw no reverse peristalsis. The tube dilated when food was forced into it and contracted again between the paroxysms of retching, giving the appearance of a bladder, filling and emptying. Some of the food was forced out through the mouth and with the help of peristaltic waves a little was returned to the stomach. Mellinger came to the conclusion that the esophagus helps a good deal in passing onward the material that it receives from the stomach during vomiting; but its activity is not absolutely essential, for animals will continue to vomit after the esophagus has been replaced by a glass tube.

The Behavior of the Bowel. As I showed in 1925, vomiting in the cat is sometimes preceded by reverse peristalsis in the bowel. This may be only an incidental part of the process or it may be one of the many factors that produce nausea and serve to start the vomiting reflexes. That such reverse peristalsis is present in men and women can be seen from the fact that they will sometimes vomit large amounts of fluid a few minutes after the stomach has been well washed out. This fluid is often bile-tinged, or tainted with feces or enema material, showing clearly that it has come from the lower bowel. It is suggestive also that when the Malays get seasick and vomit for a while, they begin to bring up some of their roundworms. W. J. Mayo (1926) has pointed out that patients with intestinal obstruction may, when they are anesthetized for operation, drown in regurgitated material.

Several years ago I was studying the intestinal contractions of a man with a jejunal fistula. He happened to vomit one day when I had a balloon in him, and it was clear from the record that there had been a marked increase in the tone and activity of the bowel for two minutes before retching began. On another occasion he vomited the egg-milk mixture that he was getting through his fistula, which showed that the direction of intestinal peristalsis had been reversed (see also Lehman and Gibson). I have seen the same sort of thing many times in animals, where a marked increase in the activity of the bowel preceded vomiting by

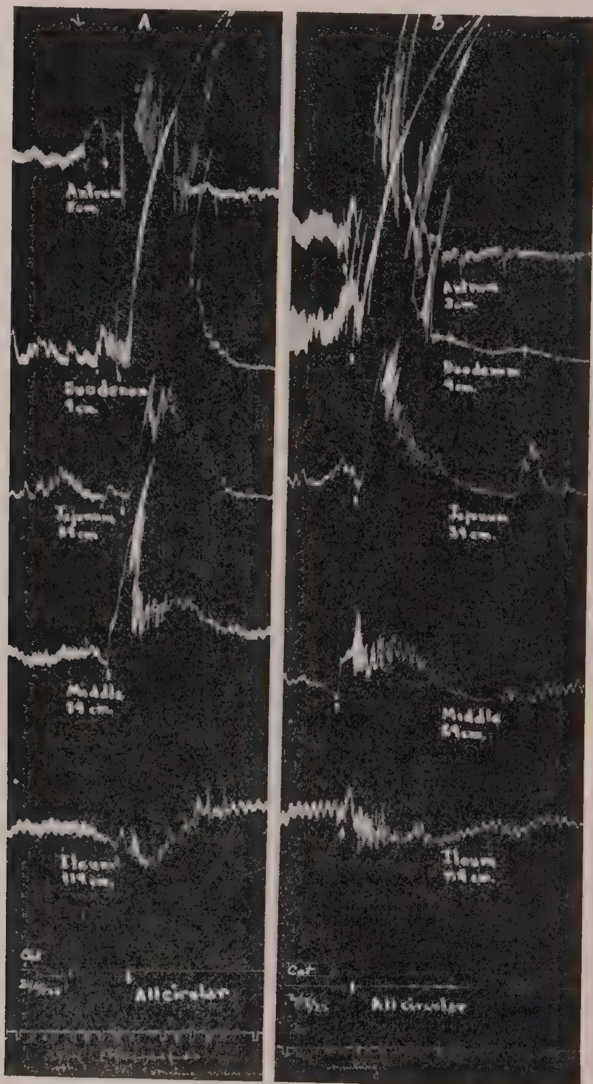

FIG. 84. Records depicting waves of reverse peristalsis in the cat's bowel preceding vomiting.

several minutes. Figure 84 is a graphic record of such an occurrence. There it will be seen that vomiting began about the time that waves of reverse peristalsis in the bowel reached the stomach.

Openchowski and Boldireff (1904[b], p. 489) noted years ago this association between vomiting and increased activity in the bowel. Ewald (1907) also, comments on a fact that I have since observed, that in ileus the stomach is filled with regurgitated material for some time before fecal vomiting appears. It is suggestive also that when stretches of bowel are operatively reversed in dogs, so that the peristaltic current is directed backward toward the stomach, the animals will vomit unless fed very carefully (Kelling 1900, p. 326).

Some physicians think that bile that has regurgitated into the stomach is the cause of vomiting, but as was pointed out in Chapter XVI, this has been many times disproved. As will be seen later in Chapter XXV, nausea is commonly produced by reverse peristalsis in the upper bowel.

The Vomiting Center. I shall not attempt here to review the older work on the subject because so much of it has been superseded by the careful studies of Gold and Hatcher. According to them, in cats, the one part of the brain that seems to be essential to vomiting is the sensory nucleus of the vagus. That this is probably the "vomiting center" is shown also by the fact that the application at this point of minute amounts of apomorphin (0.000,1 mg.) will promptly produce emesis in the dog. Although there are many things about this center that are definite, there are many others that are very confusing, and anyone who attempts to analyze the observations made, particularly on the action of emetics, will run into a maze of puzzles. Hatcher mentions the fact that some central emetics like apomorphin produce vomiting when they are applied directly to the center, while others which seem just as "central" in their actions, because they produce vomiting in the eviscerated dog, have no effect when applied directly.

Actually, it is yet a question whether we are justified in speaking of a vomiting "center," but it is certainly convenient so to designate that area in the brain which is essential

to the vomiting process in that it receives afferent emetic impulses, discharges efferent ones, and coordinates in an orderly sequence the various movements and inhibitions necessary for emesis, such as closure of the pylorus, contraction of the lower part of the stomach, relaxation of the fundus, cardia, and esophagus, closure of the glottis, stoppage of respiration, stimulation and inhibition of the diaphragm, and stimulation of the abdominal muscles.

Mellinger showed that the completely pithed frog can vomit after the administration of tarter emetic, but in that case the stomach empties through its own efforts. It appears then, that at least in lower forms of life a type of regurgitation can take place in the absence of the center, but it is doubtful whether true vomiting could ever be produced.

For many years it was taught that a drug that induces vomiting on intravenous injection must act either directly on the center or reflexly through the digestive tract; but it is now recognized, through the work of Hatcher and his associates, that this is not necessarily true, and some drugs like tartar emetic and digitalis produce vomiting mainly through their action on the heart.

The Pathways for Afferent and Efferent Impulses. Much of the research work done in this field is of doubtfnl value on account of the great difficulties in interpretatiou. Operations on the brain, cord and nerves are accompanied by shock which, at least for a time, can so depress the activity of structures near the wound that erroneous conclusions are likely to be drawn. Furthermore, anesthetics are disturbing and drug actions are uncertain. Even the position in which the animal is held during the experiment may make all the conclusions of the experimenter valueless, as in the case of cats which vomit only with difficulty when placed on their backs.

Such observations probably explain some of the mistakes of the earlier workers who, for instance, came to the conclusion that emetics like mustard, which act peripherally, are without effect after the vagi are cut. According to Hatcher this is not so, and several workers have seen vomiting in cats and dogs given copper or zinc sulfate after

vagotomy. The vagus, nevertheless, is probably the most important path for afferent emetic impulses, because Miller has shown that its destruction interferes with the production of vomiting more than does the cutting of the splanchnics. It interferes also with the production of the deep respiratory movements and the salivation that precede the act of retching. Cutting the vagi makes vomiting more difficult also because then the cardia does not relax properly. Just why vagotomy should prevent vomiting when tartar emetic is put into the stomach but not when it is put into the duodenum is not so clear. It is but one example of the many puzzles that confront the student in this field.

That impulses go to the vomiting center along paths other than those in the vagi is shown also by the fact that vomiting can be produced by stimulation of many organs not supplied by those nerves. Furthermore, many experiments by Hatcher and Weiss have shown that the afferent and efferent paths involved in the process must run in both the vagi and sympathetics. How complicated the subject is will I think be made evident by a perusal of the following table taken from a paper by Hatcher (1924, p. 499).

TYPES OF AFFERENT PATHS FOR EMETIC IMPULSES BASED ON THE PHARMACOLOGIC BEHAVIOR OF THEIR SENSORY ENDINGS.[1]

A. Sympathetic Trunk, Stellate Ganglion and Cord

1. *From the stomach, stimulated by small doses of mercuric chlorid, paralyzed by ergotoxin, not by atropin.

2. From the stomach, stimulated by large doses of mercuric chlorid, not paralyzed by ergotoxin or atropin (possibly the same as No. 1).

3. *From the heart, stimulated by digitalis, paralyzed by ergotoxin, not by atropin.

4. *From the heart, stimulated by digitalis, paralyzed by ergotoxin and atropin.

[1] Further investigation will almost certainly increase the subdivision, and it is probable that some which are here placed in different groups may be found to have only minor quantitative differences in behavior. Those marked with an asterisk are apparently common to the vagus and sympathetic.

5. *From various parts of the body, conducts normal impulses that cause emesis only when the center is hyperexcitable; paralyzed by ergotoxin, not by atropin.

B. Vagus Trunk

1. *From the stomach, like No. 1 in the sympathetic.
2. From the stomach, stimulated by tartar emetic, paralyzed by atropin, not by ergotoxin.
3. From the duodenum, stimulated by tartar emetic, not paralyzed by atropin.
4. From the heart, stimulated by tartar emetic, paralyzed by atropin (may be like No. 2).
5. *From the heart, stimulated by digitalis, paralyzed by ergotoxin, not by atropin (may be like No. 3 in the sympathetic).
6. *From the heart, stimulated by pilocarpin, paralyzed by atropin and ergotoxin (probably like No. 4 in the sympathetic).
7. *From various parts of the body, conducts normal impulses that cause emesis only when the center is hyperexcitable; paralyzed by ergotoxin, not by atropin (probably similar to No. 5 in the sympathetic).

The Association between Vomiting and Diarrhea. Hatcher and Weiss (1923) have found in the floor of the fourth ventricle, close to the vomiting center, an area which apparently serves as a center for defecation because the application there of drugs that produce nausea and vomiting frequently causes defecation also. These observations are of interest because vomiting and diarrhea are so often associated in conditions like seasickness, acute heart failure, or fright, in which the vomiting center is probably much involved.

As I have pointed out in Chapter XXIV, however, the emptying of the digestive tract in both directions may perhaps be due sometimes to a great rise of tone in the jejunum where it receives a large branch from the vagus; and at other times, as in fright, diarrhea may possibly be due to an outpouring of adrenalin. As Hatcher and Weiss suggest, there is much in common between the acts of vomiting and of defecation: both need a reflex mechanism to correlate the

activities of the voluntary and involuntary systems, and both are made up of mixtures of contractions and relaxations.

Practical Applications. Probably one of the most helpful points that the physician can get from the work of Hatcher and his associates is that afferent impulses are constantly streaming in to the center from all those parts of the body in which emetic stimuli can arise. Ordinarily these impulses have no effect because they are subliminal, but if the center should become more sensitive, as under the influence of a drug, some psychic impression, or great fatigue, then they would be sufficient to produce vomiting. Hatcher and Weiss were led to this view by observing at times in animals a sudden inhibition of vomiting due apparently to a lowering of the irritability of the center, associated with an increase in the activity of the adjacent centers for scratching and defecation. They believe that apomorphin acts on the vomiting center much as strychnin acts on the synapses in the cord (see Chapter III); that is, it helps the impulses to spread from one neuron to another.

We see then why the nausea and vomiting of nervous, hypersensitive women can often be stopped by the giving of a drug like luminal which lowers the excitability and conductivity of the centers in the brain; stimuli may still be streaming in from a pregnant uterus, a dilated heart, or a diseased gallbladder, but they are less likely to initiate the reflexes that bring about vomiting.

Vomiting Not Always Prevented by Keeping Drugs Out of the Stomach. Another important lesson that the practitioner needs to learn is that vomiting cannot always be avoided, as he supposes, by keeping a drug from dissolving in the stomach. Actually, there is considerable evidence to show that the gastric mucous membrane is less likely to be irritated by drugs and foods than are the duodenum and jejunum; and that is what we should expect because, as was shown in Chapter XVII, the stomach is particularly designed to receive and retain irritant substances until they are so neutralized and diluted that they will not injure the much more sensitive mucous membrane of the bowel. As we should expect from this, many workers, among whom I will mention Palmer

(1926[b]), Klein (1926, p. 1233), Luckhardt, Phillips and Carlson, Hirsch (1893[b]), and Wheelon and Thomas (1922), have shown that nausea and vomiting can be produced more easily by putting irritating substances into the upper bowel than by putting them into the stomach.

It is doubtful, therefore, whether the efforts that we so often make to avoid nausea by giving drugs in salol- or keratin-coated capsules are warranted. So far as I can learn, the practice is based on an ancient and erroneous theory, and unless it can justify itself by results obtained, it ought to be given up.

Actually, it appears from all the experimental work that has been done on the subject that whenever we have to give an irritant drug, we really should desire that it remain for a while in the stomach where it can be diluted and then passed gradually into the bowel. Besides, it is now recognized that most of the drugs with emetic by-effects act on the center as well as on the digestive tract, so it would seem useless to try and give them by rectum, by vein, or in salol-coated capsules. There are some curious features, however, about the behavior of some of the emetic drugs which make it advisable always that we base our practice, not on theory, but on what we can learn from actual experiment. Thus, as Guinard has pointed out, morphin has a greater tendency to produce nausea when given subcutaneously than when given intravenously. In the first instance it is absorbed so slowly that it has time to exert its nauseating effect; in the second the dose reaching the brain is so large and the depressant action on the center so great that the emetic effect is blocked and covered up.

Influences Coming from the Heart, Inner Ear and Stomach. Studies by Hatcher and Eggleston, and Weiss have shown also that a number of the drugs with emetic by-effects can act on the center by way of the heart. Thus if all the cardiac nerves are cut, digitalis will no longer produce vomiting, but another type of emetic like mercuric chlorid will still be effective; and in the eviscerated animal with no digestive tract, tartar emetic will produce vomiting only when the vagi are intact (Weiss and Hatcher).

According to W. Lehmann, deaf and dumb persons with disease of the inner ear, animals with bilateral destruction of the eighth nerve, and infants do not get seasick. This fits in with the well-known fact that disturbances of the inner ear, as in Meniére's disease, are associated with vomiting.

That influences from the bowel are more effective in producing emesis than influences from the stomach has been suggested not only by animal experiment but by the fact that vomiting is often absent in cases of gastric ulcer and carcinoma (without obstruction), while it is often severe with subacute appendicitis, volvulus of the sigmoid and intestinal obstruction.

Reversal of the Intestinal Gradient. Cohnheim and Dreyfus (1908[b], p. 56) and others have produced vomiting in dogs by distending balloons in the intestine. They found that a slowing of gastric emptying could easily be effected by an irritation of the bowel, whereas it was not observed after the production of a severe gastritis. Hirsch (1893[b], p. 380) produced vomiting in dogs by giving solutions of organic acids. Acetic acid was most effective, apparently because it had the least action on the stomach and the most marked stimulating effect on the intestine. The regurgitation of bile-stained contents into the stomach showed that the gradient was upset. Lactic acid, which had less effect on the gradient, produced only a delay in gastric emptying.

Pregnancy. As is well known, vomiting is often observed in pregnancy, particularly during the first few months. Obstetricians generally distinguish between the milder cases in which the cause is said to be "reflex," and the severer ones in which the cause is probably a toxemia. I have been impressed by the fact that nausea and vomiting very similar to that in pregnancy can occasionally be observed in women whose pelvic organs are kept irritated, inflamed or abnormally hyperemic by unsatisfactory suspension operations, by fibroids, pus-tubes or diseased ovaries. These lesions keep the uterus hyperemic, much as it is in the first few months of pregnancy; and the symptoms disappear immediately after the operative removal of the source of irritation.

It has occurred to me that the increased activity and vascularization of the uterus in pregnancy and in the presence of inflammation might in some way raise the tone and irritability of the lower part of the bowel, and thus reverse the gradient. So far I have been able to study the gradients in only a few pregnant animals. In most of these there was little change shown in the rhythmicity of the excised segments; and it is only suggestive that in a few animals studied with the abdomen open under salt solution the rhythmic gradient was markedly flattened by an increase in the rate of the ileum. That the gradient in pregnant women is flattened is suggested not only by the vomiting but by the regurgitation of acid gastric contents into the mouth. Some women will suffer during one pregnancy from vomiting and during another from severe heartburn.

It is possible that the lower bowel shares in the hyperemia of the pelvic organs. There may also be a spread of "tone" along the pelvic nerves. Elliott and Barclay Smith (1904, p. 282) found that stimulation of these nerves will raise the tone of the mid-region of the colon and will increase the tendency to reverse peristalsis there. Quite a few women notice a tendency to diarrhea on the first day of menstruation, and there again we have evidence of some effect transmitted from the hyperemic uterus to the bowel. The fact that a uterine hyperemia from any cause may upset the intestinal gradient makes me feel that the action in pregnancy must often be direct and not, as commonly assumed, by way of toxemia.

The tendency to the reversal of peristalsis in pregnancy was well recognized years ago by Campbell. He states clearly that a pregnant woman or a woman with pelvic disease has an irritable tract in which "response is usually by inverted rather than by direct action: eructation, regurgitation, nausea, vomiting, constipation, far more frequently than diarrhea and other manifestations of downward action. The tract gets into the habit of retrostalsis." The stormy vomiting and dynamic ileus seen sometimes after pelvic operations may be due to a great and sudden increase seen occasionally in the irritability of the colon.

One may perhaps explain in this way the vomiting seen sometimes after injury to the testicle (L. R. Müller, 1912, p. 37) and the upsets in digestion seen in men with enlarged prostates and distended bladders (Peyer, 1890, p. 3182; Herschell, Hutchison, Austin, 1916, p. 52). These troubles seem to correspond closely with those observed in women with inflamed and gravid pelvic organs. Many will say that these things are purely "reflex," but that word does not help us much; and I think we are justified in looking for a simpler explanation.

Vomiting can sometimes be stopped by giving solid food which may act perhaps by raising the tone of the stomach and restoring the downward gradient. Liquids often fail to stop vomiting, perhaps because they tend to run directly into the intestine without affecting the stomach very much.

CHAPTER XXIV

PRACTICAL APPLICATIONS OF THE GRADIENT IDEA

If the downward gradient is of any value to us in health, it follows as a corollary that upsets in it should produce symptoms of disease. As will be seen later, such upsets have been observed repeatedly in animals, and it is highly suggestive that most of these animals were sickly; some of them were refusing food, and others were even vomiting. The main question then before us is: Are these upsets ever present with the digestive troubles of man, and if so, are they responsible for the disturbances in motility which are then observed?

Unfortunately, these questions cannot yet be answered with certainty. Other factors may easily be more important in some cases. Thus a general increase in the irritability of the bowel might have more to do with the production of a diarrhea than a steepening of the gradient, and other factors about which we know little may be at work. On account of these gaps in our knowledge much of what follows must of necessity be purely theoretical or based on analogy. It seems to me, however, that so long as the reader will keep separate in his mind that which has been proved and that which is merely suggestive, it can do no harm to set forth in a logical manner the various ways in which the gradient might theoretically be upset, and the ways in which such upsets might affect the motility of the tract. After that has been done, it will be easier to analyze the disturbances actually observed with various lesions, and to see whether or not they agree with those to be expected from the theory. It is most encouraging to find that they do agree remarkably well in many cases; so well that we now have an easy explanation for many of the observations that have long puzzled the gastroenterologist, the roentgenologist, and the surgeon.

In many places during the following discussion I may use the word gradient, although the plural, *gradients*, may be a more appropriate term. Perhaps it is a distinction without a

difference, because the several gradients are probably all related and interdependent. As I have stated before, my impression is that the metabolic gradient is the underlying one, and it may be that disturbing factors affect it primarily and the others secondarily. I have not as yet sufficient evidence to show that they all change together under the same influences. In a number of the sick animals I have found badly upset gradients of CO_2 production, catalase content, and latent period, with a fairly stable rhythmic gradient. It must be remembered that most of these measurements were made on excised segments, and it may be that the greater amount of trauma and handling incident to the demonstration of the first mentioned gradients served to bring out latent weaknesses in the muscle—weaknesses which did not appear under the more advantageous conditions maintained during the counting of the rates of contraction. Thus, for the CO_2 estimations, the muscle is stripped from the mucous membrane and is not supplied with sufficient oyxgen; for the catalase estimations it is minced, and for the latent period measurements it is kept in a moist chamber; but in counting the rates of rhythmic contraction one can use either the intact animal with the abdomen opened under salt solution, or excised segments of bowel contracting in warm oxygenated Locke's solution.

FACTORS ALTERING THE GRADIENT

1. Irritating Lesions. These include traumatization, inflammation and ulceration (*a*) in the muscle lining the tract; (*b*) in the mucous membrane; (*c*) in the serous coat; (*d*) possibly in the nervous plexus, and (*e*) in the neighboring organs connected with the tract such as the appendix, the gallbladder, liver, pancreas, and Meckel's diverticulum. We must think also of inflammation, overactivity and vascular engorgement of the organs lying close to the digestive tract, such as the uterus, the urinary bladder, the prostate, the spleen, and perhaps the kidney.

These lesions may affect (*a*) the *metabolism*. It has been shown by M. Segale that inflammation raises the metabolic

rate of tissues. They become warm because the increase in the rate of oxidation calls for a larger blood supply, and this warms the tissues much as a heating coil would. Cutting or bruising a tissue also raises its metabolic rate. Thus, in planarian worms, Child (1914) found that cutting increased the rate for about twelve hours. (See also Hyman, 1919[c], p. 76.) We know also that a bruised part becomes electronegative to the neighboring healthy tissue and, as I have noted before, that indicates an increase in the chemical activity (Lillie, 1917, p. 181). As Lillie (1914, p. 441) has pointed

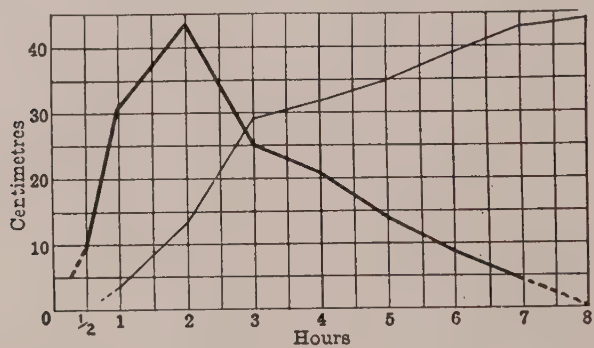

FIG. 85. The heavy line represents the amounts of potato-bismuth mixture present in the bowel at successive hours after feeding. The light line represents the amounts after croton oil had been injected into the colon. (*From Cannon.*)

out, local injury produces demarcation currents which extend in both directions along the muscle. They exert not only electrotonic blocking influences, but they may directly compensate the action current of an approaching excitation wave and so prevent its effect from extending beyond the point of injury. Garrey believes that this mechanism probably accounts for the formation of heart block when only a few fibers in the bundle of His are injured by a pinprick.

An increase in the metabolic rate will raise (*b*) the *rate of rhythmic contraction.* Taylor and I showed that the rate of contraction of an excised segment of bowel varies with the temperature just as a chemical reaction will vary. Once, on

opening a rabbit under salt solution, I found a badly inflamed Peyer's patch in the ileum. The affected loop of bowel was cut out and segments from it were put into warm aerated Locke's solution. It was found then that the segment just above the lesion contracted from 21 to 25 times per minute, or more than twice as fast as it would normally have done (Alvarez, 1918[a], p. 347).

Inflammation ordinarily increases (*c*) the *irritability* of a tissue. That it increases (*d*) the *tone* of smooth muscle is easily demonstrated in the digestive tract. The hourglass contraction opposite the site of a gastric ulcer is due partly to the increased tone of the muscle fibers which are stimulated directly by the lesion. The same local action produces the puckered and irritable cap of duodenal ulcer, or the tightly closed sphincter with fissures of the anus.

2. Ingestion of Food with Distention of the Bowel. All parts of the tract are distended at times by gas; the stomach is distended by food; the small intestine by partly digested material, and the colon by feces, or by enemas. We have seen that distention of smooth muscle generally causes it to contract more actively. A greater activity means (*a*) a *faster metabolism*. That, together with the distention, may increase (*b*) the *rate of rhythmic contraction*. Distention alone will increase the rate in primitive types of hearts (Straub, 1904), and I have some evidence that the same thing happens in the bowel. I cannot say as yet just how distention and increased activity affect (*c*) the *irritability*, but I do know that after a loop of bowel full of food has been segmenting actively for a while it gets on a "hair trigger" so that a slight stimulus is sufficient to start a peristaltic rush.

The activity incident to digestion has a pronounced effect on (*d*) the *tone*. Mall (1896[b], p. 45; see also Cannon, 1911[b], p. 421) pointed out years ago that "when the intestine is at rest it is anemic, small and long; when digesting it is hyperemic, large and short." I have placed two markers 3.5 cm. apart on an active and apparently stretched piece of bowel, and have found them 8 cm. apart later when that region had emptied and quieted down. Cannon ascribes some of this shortening with activity to the "contraction remainder"

of smooth muscle; that is, after each contraction the muscle does not relax quite to its previous length.

3. Nervous Stimuli. Although the digestive tract is largely autonomous, there are undoubtedly many times when the extrinsic nerves affect the progress of material through it. Theoretically these nerves can depress or stimulate the tract as a whole; they can depress or stimulate one part more than another; or they can depress in one place and stimulate in another. There is some experimental evidence that stimulation of the vagi will affect the two ends of the stomach differently (May; see also Fig. 3 in this book). Some have observed a relaxation of the cardia with an increased activity near the pylorus. This would naturally tend to reverse the gastric waves. Spadolini has shown also that stimulation of the vagi or of the splanchnics often produces effects which are unequal or dissimilar in different parts of the bowel.

Similarly in the heart of the turtle, the sequence of the beat may be upset by stimulation of the vagus, which depresses the sinus while it increases the automaticity of the funnel region (Gault). Wilson produced nodal rhythm in a number of young men and women by stimulation of the vagus, after the giving of atropin. Apparently the nerve endings in the A-V node were more affected by the drug than those in the S-A node. Under these circumstances stimulation of the vagus would tend to reverse the gradient by depressing the sinus more than the ventricle. T. Lewis (1920, p. 194) states that vagal stimulation alone is sufficient to displace the pacemaker in some people; and F. R. Miller (p. 411) and others (S. Mayer) have found that it will cause vomiting.

There is considerable evidence for the view that a pleasurable psychic stimulus will raise the tone, particularly of the upper end of the tract, and will improve the gradient. We have no data to show that the extrinsic nerves affect (*a*) the metabolism. There is no evidence that they affect (*b*) the rate of rhythmic contraction. They probably tend markedly to depress (*c*) the irritability, so that the muscle will not respond to every stimulus. The most marked changes are seen in (*d*) the tone.

4. Toxic Depression. Theoretically the tone and activity of the muscle should be depressed by toxins of various kinds, either equally in all parts, or to unequal degrees in different parts. It is possible, also, for a toxin to depress one part while it stimulates another. If the depression is equal in all parts, the gradient will be left intact and the progress of the food may be slowed simply because of the general

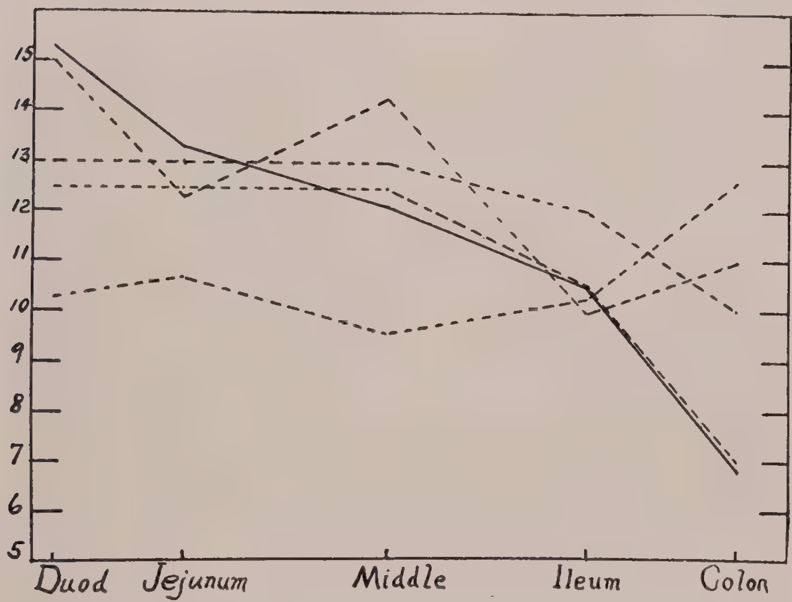

Fig. 86. Ordinates represent rates per minute; abscissas represent the segments at varying distances from the pylorus. The solid line represents the average for fifty-three rabbits. The broken lines represent data from sickly animals.

weakness and sluggishness. This generalized depression may account for the flabby stomachs and intestines which we see particularly in asthenic women. There are many reasons for believing, however, that the depression is often uneven in its distribution, and likely to alter the gradient.

Time and again during the preceding chapters I have had occasion to remark on the great difference in the hardiness of the various muscle strips (Alvarez, 1914, p. 178 and

1917[a], p. 426, also, 1917[b], p. 445, also, 1918[a], pp. 346 and 348, also Alvarez and Starkweather, 1918[a], p. 189, and 1918[c], p. 65). In the stomach the muscle in the pacemaking region near the cardia is most sensitive to handling, to electric shocks, to preservation in the ice box and to all unfavorable conditions; and similarly the muscle in the duodenum is much more sensitive to adverse conditions than is the muscle in the ileum. The muscle of the colon is more hardy, again, than that

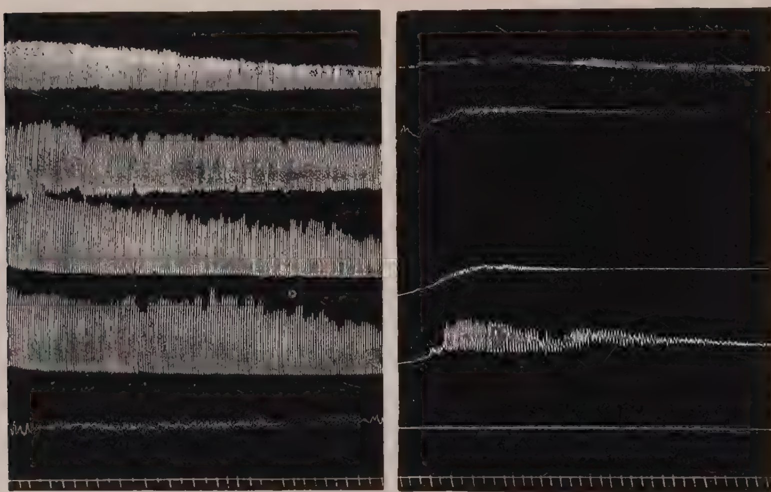

Fig. 87. Sample tracings from segments from a normal rabbit, on the left, and rabbit purged by castor oil on the right. From above downward the records are from the duodenum, jejunum, upper ileum, lower ileum and colon. The time record represents thirty seconds.

of the small bowel. It was found also that the gradients of rhythmicity, metabolism and latent period were reversed in many of the sick animals. Figure 86 shows how the rhythmic gradient may be altered. The segments were removed from rabbits which were heavily infected either with snuffles, coccidiosis or a cecal whipworm. In these sickly rabbits the segment excised from the duodenal region sometimes would not contract at all in the Locke's solution, although segments from the ileum and colon would do so satisfactorily.

Figure 87 shows the difference between the contractions of a healthy rabbit's intestine and those from a rabbit that

had been purged the day before with castor oil. In this case the amplitude is much affected. Figure 19 shows on the left the usual gradient of latent period found in normal dogs, and on the right the gradient found in distempered dogs. It is apparent that the muscle in the duodenal segment suffers most, and that the muscle from the ileum is made more irritable by the toxins, whatever they are. A similar difference was observed in the stomachs of sick animals; that is, the segment from the cardiac end was insensitive and sluggish while the segment from the pyloric antrum contracted even more promptly than it normally does. Naturally, this drop in the effectiveness of the upper end with a corresponding rise in that of the lower would tend to reverse the gradient.

It may be that the effect of some toxins is primarily a stimulating one, and that the ileum and antrum profit by it because their original tone is low. At the upper end, however, the tone of the muscle is probably so nearly maximal that further stimulation pushes it over the limit of safety, and the tissue is damaged. I have some pharmacologic evidence in favor of such a view, and there are many analogies in the biological literature.

Anyone who attempts to do any work with the intestinal muscle will I think soon be impressed with these marked changes in the sickly animals and will realize how necessary it is in such experiments to secure really healthy ones. The same precaution must be taken when studying the heart. It is well known that preparations from thin or sickly animals or from animals kept too long in the laboratory will not beat satisfactorily and that frogs and turtles should not be used during the summer or during the mating season (Stiles, p. 341; Schultz, 1903, p. 126). Hunter found that he could not use Salpae kept in the laboratory for any length of time because their hearts beat at both ends simultaneously, and Dr. Cohn of the Rockefeller Hospital tells me that a large proportion of the dogs studied in his laboratory show nodal rhythm. Eyster and Meek, Halsey (p. 731) and Cullis and Tribe remark on the same thing. Similar displacements of the pacemaker have been observed in man in various asthenic states (Williams and James). The evanescent nature of

these upsets in the cardiac gradient, and the fact that sometimes at autopsy no local lesions are found, makes me think that the displacement of the pacemaker may be

Fig. 88. The effect of asphyxia on segments from different regions. From above downward the segments are from the duodenum, jejunum, middle ileum and colon.

due to an unequal effect of fatigue or disease-toxins on different parts of the heart. It is well known to athletes that a little fatigue or infection, a sleepless night, a slight cold or diar-

rhea, will greatly diminish the efficiency of the heart and skeletal muscles.

After I had for some time been studying the upsets of the intestinal gradient due to the unequal effects of disease-toxins, I discovered that C. M. Child (1917) had been making similar observations on the lower forms of life. He argues that tissues with a high metabolic rate and a large need for oxygen must suffer more from a scarcity of that oxygen than do tissues with a low rate. The supply of the gas can be curtailed either by interfering with the circulation and pulmonary respiration or by giving a poison like KCN which keeps the oxygen from combining with the protoplasm of the cell (Hyman, 1919[b], p. 340). Child has found that weak solutions of KCN may be used very conveniently to demonstrate the presence of gradients of metabolism, because the tissues with a high rate become paralyzed and die first; and the others with slower rates follow in order. Thus if planarian worms of different ages are put into .0065 per cent KCN, the younger ones with the higher rates of oxidation die before the older ones. If Hydras are submitted to the same test the more active ones die first. Similarly, young animals and babies with their fast rates are more susceptible to anesthetics than are old animals and old men. Symes, and Glaister and Logan note that in coal mines the boys are more likely to succumb to CO poisoning than are the older men.

Following this line of reasoning, Child put into dilute solutions of KCN a small water organism which swims with the help of comblike rows of large cilia arranged along its sides. The damaging effect of the KCN was so much more marked at the pacemaking end that the impulse was sometimes left to begin at the other pole of the animal; the sequence of the beat was thus reversed, and the animal made to swim backward.

After reading about this work of Child I put five segments from different parts of the bowel into warm Locke's solution, and after they were all contracting well I shut off the air which had been bubbling through the solution (Alvarez and Starkweather, 1918[a]). Figure 88 shows how markedly

this affected the activity of the duodenum and jejunum and how little it affected that of the ileum. As was to be expected, a trace of KCN added to the solution produced much the same type of graded depression (Fig. 89).

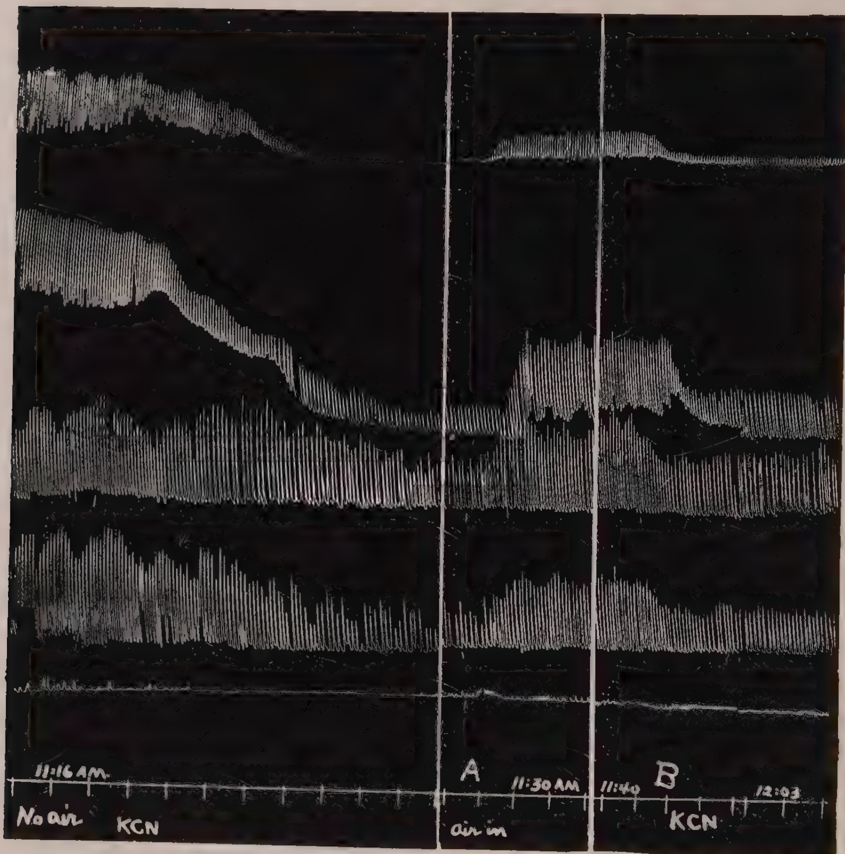

FIG. 89. Effect of KCN on segments in non-oxygenated Locke's solution. At *A* air was allowed to bubble through the solution; at *B*, more KCN was added.

It appears that the heart muscle also shows a graded response to asphyxia. We would expect the sensitive pace-making region to suffer most, and actually Lewis and Mathison have found that the auricle is slowed, the ventricle

is accelerated and dissociation is produced. These changes are brought about locally, and are unaffected by curare, atropin and vagal section. On the return of respiration, recovery is generally prompt and complete. Similarly,

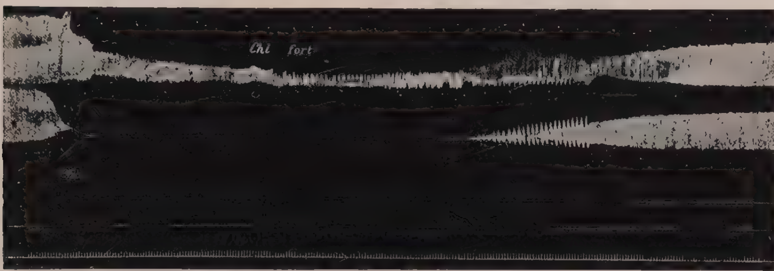

FIG. 90. The upper tracing is from the left ventricle; the lower is from the left auricle. Time marking represents records. Note greater effect of chloroform on the auricle. (*From Raasche.*)

in hibernating dormice, Miss Buchanan found that the ventricles beat alone, but as the animal wakes and begins to breathe more rapidly, the P waves (auricular) appear in the electrocardiogram. After a while the gradient is restored and the auricle takes the pace. When the animal breathes in Cheyne-Stokes fashion, the P waves disappear during the periods of apnea. Greene and Gilbert found also while studying the hearts of aviators subjected to the rebreathing test, that when the oxygen supply was greatly lowered the S-A region was the first to fail.

Raasche has shown with the excised heart that chloroform can paralyze the auricle in dosages which only decrease the amplitude of the ventricular contractions, and it may be that some of the stoppages of that organ after anesthesia are due partly to a reversal of the rhythmic gradient (Fig. 90). Some of the other cardiac poisons, and some disease-toxins may perhaps act in this disturbing way.

Tashiro has recently brought forward considerable evidence to show that anesthesia, particularly in nerve trunks, may be due to a similarly produced reversal in the metabolic gradient along the nerves. Much work must yet be done before such a theory can be generally accepted, but in view

of the many analogies, the idea is a very attractive one. He explains perfectly some of the puzzling phenomena of conduction through anesthetized stretches (Niwa).

There are so many practical applications of this idea of gradient reversal under the action of drugs and toxins, that I believe it must be used more and more as men come to know about it. It offers the simplest and easiest explanation for many phenomena which have hitherto been explained in roundabout ways, as by bringing in a complicated system of nerves, the workings of which are not really understood. I think there is no doubt that digestive upsets in the sick are due in part to influences coming through the extrinsic nerves, but when one can demonstrate a marked reversal of the gradient in small excised segments of gut, and when one can tell by studying such segments whether they have been removed from a sick or from a healthy animal, I think the most devoted follower of Eppinger and Hess must admit that the local changes have some significance.

I believe that these upsets in the gradient which are so easily demonstrated can explain the loss of appetite, the disgust for food, the nausea and the vomiting seen in infectious diseases and asthenic states. The distempered dogs and snuffling cats often refuse food. If some is forced on them it may stay in the stomach for hours or days. This has been commented upon by Cannon and others. In autopsies on people who have died with botulism, food has been found in the stomach which was eaten many days before, when the trouble commenced. Similar stagnation is often noticed in the stomachs of men and women with tuberculosis and other infectious diseases. As in many of these cases I find the pylorus patent and can see good peristaltic waves, I cannot get away from the idea of a flattened gradient. Later when such patients go on vacations, take rest cures or get over their infections, their appetites return, and they are able to digest the roughest food, because their gradients, I believe, have become normally steep again.

It is well known to all clinicians that most men with failing hearts suffer from indigestion and flatulence. Remembering the upsetting effect of asphyxia on the gradient, it

has occurred to me that a chronic passive congestion, interfering with the oxygen supply to the intestinal muscle, might easily account for much of the trouble. It is possible, of course, that some of the disturbance is due to stimuli coming

Fig. 91. The graded effect of adrenalin. From above downward the segments are from duodenum, upper ileum, lower ileum and colon.

down the vagus, but we know much less about the way in which such stimuli act than we know about the way in which asphyxia acts. Nausea is often a marked symptom in acute decompensations of the heart; and in a subsequent

chapter the reasons will be given for believing that that means mild reverse peristalsis. Nausea and vomiting are also prominent symptoms in subacute CO poisoning, in which case the intestine must share in the general asphyxiation of the tissues.

5. Drugs. Very little is known as yet about the effects of drugs on the gradient. This is due, of course, to the fact that it has not yet occurred to pharmacologists that a drug might upset the dynamic equilibrium of the intestine by stimulating or depressing one part more than another. To be sure, we speak of certain purgatives as acting principally on the small bowel or on the large, but after reading very extensively on the subject, I can find no statement suggesting that any one has thought of purgation as being due possibly to a lowering of the tone of the lower colon.

Figure 91 shows that the action of adrenalin on the intestinal muscle is a purely depressant one, and that it is graded from duodenum to ileum. I was able to show that it is a depressant also when given intravenously to man, and yet we know that it often acts as a purgative. In a woman with a large ventral hernia, which left the ileum easily visible under a thin covering of skin, adrenalin produced a transient cessation of rhythmic movements which was followed by the appearance of some peristaltic rushes, and later by a summons to empty the bowel. It seemed to me that the rush waves might have been brought about by an unbalanced condition of the gut due to the persistence of activity in the duodenum at a time when the ileum and colon were paralyzed. Magnesium sulfate is another muscular depressant which shows a graded effect on the segments, and which purges. Here, however, the pronounced effects on the absorption of fluid from the mucous membrane are probably much more important factors in producing the diarrhea.

I have studied the effects of some seventy-five different drugs on excised segments from different parts of the bowel (Alvarez, 1918[b,c]), and have found definite regional differences with many of them. Much work must yet be done, particularly on the intact animal, before we can say whether these differences have any practical significance. It is only

suggestive that a number of the drugs whose action on the segments, if duplicated in the intact animal, would tend to reverse the gradient, are emetics; and many of those that would tend to steepen it are well-known laxatives. Pharmacologists would probably remind me that almost all of the emetics have been shown to act directly on the vomiting center in the medulla, and as Eggleston and Hatcher (1915) have shown, even an eviscerated dog with no digestive tract between his diaphragm and his anus will retch when given apomorphin. It is worth noting, however, that some of the drugs, which in large doses produce emesis, in small doses produce regurgitation, heartburn, belching and nausea, which as I shall show later, are probably signs of mild reverse peristalsis. It seems to me that these drugs may perhaps first reverse or flatten the gradient in the bowel; and that the disturbances thus produced may finally so influence the center in the brain that it calls into action the voluntary muscles and brings about coordinated vomiting movements.

It is interesting that the ancients used purgatives to restore the downward gradient after they had produced too violent and too lasting an emesis, and similarly they gave emetics to stop violent purgation. When the ancient Egyptians wanted to see if a woman was pregnant they gave her pounded watermelon in milk. If she vomited, the test was supposed to be positive (Neuburger). A mild emetic insufficient to turn a healthy person's stomach might easily be sufficient to reverse peristalsis in a woman whose gradient was already somewhat upset by the pregnancy. As I have already pointed out, there is some evidence that the gradient is actually flattened or reversed in some pregnant women.

I think it is quite possible that certain laxatives, especially calomel, help the "bilious" not because of any action on the bile, for that has been disproved, but by restoring the downward gradient which has been upset, perhaps by the overactivity of a distended colon. It may be that drugs like eserin and pilocarpin which produce active peristalsis do not serve well as purgatives because they stimulate all parts of the tract equally. Katsch (p. 287) who watched the con-

tractions of the bowel through glass windows in the abdominal wall, noted that although these drugs greatly increased the activity of the muscle, they did not cause much movement of material from one loop to another.

WAYS IN WHICH THE VARIOUS FACTORS CAN ALTER A GRADIENT

Theoretically a gradient as a whole may be made more steep, less steep, level or reversed. Each of these changes may be brought about in three different ways. Thus, the gradient may be steepened by raising the activity of the upper end of the bowel, by depressing the lower end, or by doing both at the same time. The gradient may also be altered in some sections. Thus in cases of vomiting with diarrhea it may be that some point in the middle of the bowel has become very irritable so that the gradient slopes away from it in both directions. A lesion producing a slighter degree of local irritability may make only a small "hump." The gradient might also be interrupted by what may perhaps be termed "deep holes." Thus in a number of purged rabbits, short sections of bowel were found which would not react at all to strong electric currents or pinches, while the adjacent bowel on either side was very irritable. Theoretically food and gas might become trapped for a while in such weakened segments (Alvarez and Taylor).

Stimulation at the Upper End with Possible Steepening of the Gradient. It may sound like a Hibernianism, but it does seem that food goes down the tract more easily because it is put in at the upper end. A rise of tone in the stomach and duodenum tends to make the gradient of forces steeper down the bowel. There is some evidence that a barium meal will go down the bowel faster if it is followed by a second meal given shortly afterwards (Hurst, 1912; Lüdin) and this second meal probably tends to maintain the high tone at the upper end. There is also considerable evidence that pleasurable psychic stimuli still further raise this tone; and several observers have stated that contrast meals leave the stomach more rapidly if they are made

palatable (Hurst, 1912; Gilmer). Haudek and Stigler (p. 159) thought that the emptying of the stomach was slower when the food was taken with disgust. Takahashi showed that when a cat was fed with a spoon its stomach emptied half as fast as when the animal ate by itself. Sailer (Worden et al.) thought that the bismuth meal left the stomach more quickly when the patient drank it than when it was given by stomach tube. I observed in a patient with a jejunal fistula that the contractions of the bowel were more active when the patient ate by himself than when a nurse fed him; the latter method of eating was plainly annoying to him.

One of my patients with an incompetent anal sphincter generally had one or more bowel movements immediately after either eating, smelling, seeing or even thinking pleasurably of food. It has been shown also that sham drinking, particularly in thirsty animals, will cause water to leave the stomach of a dog much faster than it otherwise would (Best and Cohnheim, 1910[a], p. 116). The dog drinks in the usual way, but the water runs out through an esophageal fistula in the neck. The water in the stomach is put in through a gastrostomy opening. Such sham feeding will also prevent the backflow into the stomach that occurs when fat is introduced into the duodenum through a fistula (Best and Cohnheim, 1910[c], p. 125); it is explainable if the pleasure of drinking has caused the tone of the stomach to rise above that of the duodenum.

Jonas, several years ago, remarked on the rapid progress of food through the small intestine, and the diarrhea which may appear when the stomach empties too rapidly. Hence he speaks of the stomach as the "Hauptmotor" for the intestine. (See also Surmont and Dubus.) A similar hypermotility with even fatal diarrhea has been observed occasionally after gastroenterostomies when the stomach emptied too rapidly (Hurst, 1913[b], p. 466; Moynihan, p. 221). This steepening of the gradient by rapid overdistention of the duodenum may be largely responsible for the diarrhea of people with achlorhydria. The reason that it occurs generally in the morning may be that the bowel is then most irritable and responsive on account of the night's rest. There may, of

course, be other factors—the intestinal contents may be more stimulating on account of defective chemical digestion, abnormal temperature, abnormal osmotic pressure, or abnormal bacterial content.

If, on the other hand, gastric peristalsis is weakened and the emptying of the stomach delayed, the progress of material through the bowel is often slowed. Dagaew found in dogs that when the strong antral muscle is removed, the food reaches the lower ileum in thirteen hours instead of six. Similarly, in a human case, Cohn found that after complete removal of the stomach and vagus-endings the food took twenty-four hours to reach the cecum. Cole (1914, p. 110) has remarked also on the slow emptying of the cecum if the patient fasts after taking a barium meal.

There is some evidence that actual reversal of the gradient may take place during starvation if the tone of the upper end of the tract falls markedly. This may account for the nausea experienced by many persons when they are hungry. Boldireff (1904[a]) states that in animals that have fasted for some time, intestinal juice will often run out of a gastric fistula continuously.

There is no doubt that irritant lesions increase the tone and activity of the upper end of the tract. In the presence of a duodenal ulcer not only the duodenum, but the whole stomach often becomes irritated so that it shows four or five waves at a time. A similar hypermotility is observed in some cases of gallbladder disease and in these cases the head of the barium column is often found at the splenic flexure after six hours, which is exactly what we should expect if the gradient were to be steepened.

Theoretically a duodenal or pyloric ulcer should delay the progress of material coming toward it from the stomach, and, when irritant enough, it should reverse the gastric waves. Actually we do find in many of these cases a six-hour residue in the stomach and, more rarely, we see reverse waves. Occasionally I have seen wavelike contraction-rings arising in the stomach, perhaps moving downward a few centimeters and then fading out as if they were blocked from advancing farther. Unfortunately the picture is com-

plicated by a number of factors, one of which is probably the presence of a connective-tissue barrier at the pylorus which not only stops the progress of the waves downward, but tends to block some of the influences passing upward.

Many of the six-hour residues are due almost entirely to a mechanical blocking of the pylorus by the lesion. In other cases we find that the stomach empties unusually rapidly during the first few minutes, and after that, there is marked stagnation for hours. In these cases, it seems to me that the hypertonic stomach, distended and stimulated by the food, is able to overcome the back pressure from the ulcer. After that stimulus is partly gone, the spasm produced by the ulcer, together with the change in gradient, is able to hold back a residue in the stomach, sometimes until that organ is again distended by food.

When a stomach is greatly distended, owing to the presence of a stenosing ulcer at the pylorus, the point of origin of the waves may be affected also by differences in the pressure sustained by different parts of the muscular wall. Other factors will be found discussed in Chapter XII. Carcinoma ordinarily seems to grow without irritating the surrounding muscle very much; in fact, it may even depress it; hence it is, perhaps, that in the presence of such a lesion the gradient often remains normal, and symptoms are not produced until the tumor produces a mechanical obstruction.

As has been shown in Chapter XVII, there are many things about the behavior of the pylorus which can best be explained on the basis of a gradient of forces between the stomach and bowel. Any stimulus that increases the tone and activity of the stomach shortens the emptying time, and anything that tends to irritate the duodenum lengthens that time.

Stimulation in the Middle. We have seen that a stimulus that raises the tone in the middle of a loop sends off waves in both directions. Hence it is not surprising that food put into the middle of the tract tends to go both ways. Thus in jejunal feeding, unless the food is put in slowly and at body temperature, there will often be nausea, regurgitation of the material, and even vomiting. In certain cases I observed that the patient's discomfort was relieved only by giving a little

food by mouth just before the feedings. This perhaps raised the tone of the stomach to its normal position above that of the jejunum. In one such case I saw nausea, vomiting and colic produced by giving a Murphy drip of glucose and salt solution. When this was stopped, the patient had no further distress until one day when he had a cleansing enema. This may have served to raise the lower end of the basic gradient of the bowel.

It is common knowledge that vomiting is often associated with diarrhea. Thus, a small boy who had eaten his fill of blackberries vomited three-fourths of the amount twelve hours later, and shortly after that the remainder was voided in loose bowel movements. Probably enough of the irritant material got into the jejunum at the start to raise the irritability there and prevent the stomach from emptying. Finally the tone became high enough in the upper bowel so that it could clear itself in both directions. The vomiting and diarrhea with seasickness or after strong psychic stimulation might be due, at least in part, to a rise in tone of the jejunum at the point where it is so richly supplied with vagus fibers (Bayliss and Starling, 1899, p. 141; Mackenzie, 1916 and 1917, p. 287; and Jacobj, 1891, p. 198).

Lesions in the course of the bowel may make the affected area so irritable that the barium meal will stay out of it (Stierlin). Thus Kienböck, and Case (1915[c], p. 381) have remarked on the emptiness of the cecum in some cases of cecal tuberculosis. Nothnagel (p. 39) found that the food was rushed through sections of bowel which he irritated by the injection of concentrated salt solution, and White made similar observations after injecting croton oil into the cecum.

If, as the theory demands, the gradient is reversed above an irritated place in the bowel, we should expect the "reversed" segment to remain empty, and actually we do find that food does not pack up against an obstructed place unless the blockage is due to a carcinoma or some other slowly arising and non-irritating cause, that is, something that does not affect the gradient (Kirstein, Kelling 1903, Maleyx, Reichel, Nothnagel p. 29, Quirot p. 25, and Shimo-

daira). The more irritating the lesion, the wider is the empty zone, and the farther orad are the signs of back pressure.

Intestinal Obstruction. Years ago Kirstein came to the conclusion that the symptoms of acute ileus are not the result of closure of the bowel but of its maltreatment; when he cut the ileum across and sewed it up, food went on down and packed against the obstruction and the dogs were not sick. When, however, he pinched the bowel with an elastic ligature the food was held back far above the lesion and the dogs were very sick. Treves (1902, p. 2) noted also that in acute intussusception violent symptoms of obstruction often appear, although at operation little narrowing is found in the lumen of the bowel.

In other cases of intestinal obstruction no organic narrowing can be found, and the cause is said to be "dynamic." The following experiment shows that intestinal obstruction can occur without any narrowing of the lumen at all. I took a rabbit's intestine, exposed under salt solution, and pinched the lower ileum with a hemostat, so as to bruise a narrow ring. The diameter of the lumen was in no way altered. The abdomen was closed; the animal was kept under urethan anesthesia, and was opened again several hours later. It was then found that no food had passed the injured place, although the bowel above was markedly distended and was contracting violently. Waves approached within 10 or 15 cm. of the site of the lesion, where they either faded away or broke against reverse waves. The bowel immediately above the lesion contained only gas. I concluded that the gradient was uphill for some distance above the bruised tissue. Kelling (1903) was actually able to show such a reversal in the gradient of intra-intestinal pressure by tying manometers into the bowel at different levels above an experimentally produced obstruction.

The fact that the segment of bowel immediately above the site of obstruction contains nothing but gas has been commented upon by some surgeons who have come to the conclusion that in bad cases, enterostomies should be made high above the lesion if any drainage of fluid is to be expected. Other surgeons have noticed that gastric stasis dilatation and

appear early in the course of intestinal obstruction; they have washed large amounts of intestinal contents out of the stomach some time before the reversal of the gradient was marked enough to produce fecal vomiting (Ewald, 1907). We see then that the gradient idea throws great light on the peculiarities of intestinal action in ileus, and in its turn, receives support and confirmation.

Stimulation at the Lower End. The commonest lesion found at the lower end of the small intestine is appendicitis. This disease can produce all grades of back pressure from a slight ileac stasis, demonstrable by the roentgen ray, to the vomiting of large amounts of intestinal fluid. Just as the emptying of the stomach tends to produce an emptying of the lower ileum into the cecum (Hurst, 1909, p. 34, also, 1913[a], p. 55), so it appears that an early emptying of the ileum may favor the emptying of the stomach, and a late emptying of the ileum may slow the emptying of the stomach (Cole, 1914, p. 109; Barclay, 1915, p. 643). Considerable experimental work has been done on the subject by Hedblom and Cannon, and White. They found that in cats they could slow the progress of food through the stomach and small intestine if they irritated the cecum sufficiently with croton oil. Mild degrees of irritation produced no effect on the emptying of the stomach.

Similarly in man, much depends upon the degree of irritation produced by the lesion, upon the stage in which we find the disease, and upon the original stability of the gradient in a particular individual (Borgbjärg, Barclay, 1913[b], Paterson, p. 197). Thus in an interval between attacks we may be unable to detect any abnormality in the fluoroscopic picture; with a subacute inflammation there may be loss of appetite, nausea, and some gastric and duodenal stasis, and in an acute attack there may be persistent vomiting. I remember, however, a strong, stout young woman with a good appetite, who walked around for several days with an "exploded" appendix. Even during the height of her pain she had no nausea, she did not vomit, her appetite remained good and she noticed only a coated tongue, a bad taste, a tendency to fill up quickly after eating, and some diarrhea.

Apparently the gradient of this robust girl was so good that even a pericecal abscess could not reverse it. All it could do was to steepen the gradient below the lesion. Theoretically, we should always find a more rapid emptying of the colon with appendicitis, and we do see it quite often in children. According to Deaver (pp. 226 and 244), it is present in adults in only 13 per cent of the cases; in them, apparently other factors neutralize the tendency.

Some of the most violent forms of reverse peristalsis in the tract are due to the irritation of the sigmoid flexure caused by volvulus. I once saw a woman who, after eating shell fish, vomited so violently and so continuously for about a week that she died. At autopsy the only thing that could be found was a small patch of markedly inflamed mucous membrane in the sigmoid flexure. Vomiting can be produced by irritating or distending the colon with enemas. Several writers (Rolleston and Jex-Blake, Bine and Schmoll) have commented on the vomiting which not infrequently occurs with rectal feeding. The more irritating the enema is, the more likely it is to cause trouble. Several of my patients get nausea with ordinary injections of water or physiologic salt solution, but they vomit when soap, glycerine, turpentine or glucose is added to the solution. I have long felt that the Murphy drip is responsible for some of the distress and nausea suffered by patients after abdominal operations, and my experience makes me feel that it should be used only when necessary to replace water lost by bleeding and vomiting. Especially after operations in the pelvis, nothing should be put into the rectum that can raise its tone still farther and so upset the gradient.

Constipation. As has been pointed out in Chapter xx, constipation is probably due at times to an increase in the irritability and tone of the rectum and anus, an increase that tends to reverse the basic gradient in that region and to keep the feces from coming down far enough to start the reflexes concerned with defecation.

Depression at the Lower End. As yet we know very little about alterations in the gradient due to depression at the lower end. I have seen some cases in which diarrhea

seemed to me to be due almost undoubtedly to the loss of tone of the lower end of the bowel following extensive operations for fistula in ano. In these cases, every stimulus from above produced a bowel movement. Normally, such stimuli produce a surge toward the rectum which is taken up or thrown back by the tonic state of the lower bowel. If this influence is removed by making a large fistula into the lower ileum, the food will go through the small intestine too fast (Demarquay, Macewen). It is suggestive that in most cases of diarrhea the colon is atonic. This can be seen not only with the roentgen ray but it shows itself also in the ease with which a sigmoidoscope can be thrust far into the bowel. On the other hand, in the constipated, the anal sphincters and sometimes the whole rectal wall are exceedingly tonic; the roentgen ray shows a narrow lumen with marked haustration, and the sigmoidoscope is gripped firmly. A serious objection can be found to this line of argument in the work of Müller and Hesky, quoted in Chapter xx. Theoretically, the removal of the colonic muscle might easily cause diarrhea, but according to these investigators, such diarrhea is transient and generally gives way to slight constipation. The problem must be studied further.

An Illustrative Simile. Some who find it hard to understand what a gradient of forces is, and who have difficulty in following the argument as I have outlined it in the preceding pages may perhaps be helped by the following somewhat grotesque simile:

Let us imagine a game of push-ball played by a column of men who have been graded according to their metabolic rates. At one end they are young, wide awake and active; at the other end they are old and comparatively sluggish in their movements. These men will represent the muscle fibers along the bowel. The first young man takes the ball and tries to push it past the second. The second resists, but is soon overcome owing to the greater activity and aggressiveness of Number 1. As soon as the ball passes Number 2 he joins with Number 1 in trying to push it past Numbers 3 and 4. Once past them, Number 1 and Number 2 rest while Number 3 and Number 4 push it past Number 5 and Number 6; and

so it goes. The men in the first third of the line (jejunum) play incessantly so long as the ball is near them, and they soon force it down among the old men. These play only at intervals, often letting the ball lie quiet while they rest. New balls are sent down the line from time to time so that the old men generally have three or four on their hands at once. They are aroused to get rid of one or two of these when they see that a new one has started down (gastrocolic reflex and defecation).

Usually the ball moves in one direction and there is little likelihood that the old men with their intermittent efforts will ever overcome the youths; but one day some of the old men are so stimulated by some drug that they play fast and furiously, and the others cannot push the ball anywhere near the lower goal. On another occasion some of the old men are injured and this stimulates their comrades to greater efforts so that the injured ones will be relieved for a while from the trouble of handling the ball. Their efforts may be so strenuous that the balls are thrown out the way they entered. On still another occasion, a cloud of poison gas is liberated over the players. All are weakened and some become ill, but the young men who breathe faster are more susceptible to the poison and suffer more from the lack of proper air than do the old men. Until they recover, the game is slower, but the old men are now relatively more active than the young ones and the ball is sometimes sent back to its original starting place.

A change in the play is brought about also when the balls are made unpleasant or painful to handle. Perhaps they have been filled with pepper or studded with sharp spikes. The first one or two to start down the line are rushed through, so that the players can get rid of them as rapidly as possible. The men are then so irritated by this annoyance that they throw back the next few balls that are offered them (diarrhea and vomiting).

Some physicians at first confuse the gradient of forces with the gradient of gravity due to the position of loops of bowel in the abdomen. Returning to the simile, it will be seen that if the game of push-ball is being played on the

side of a hill it will make little difference whether the young men are above or below the old. The position of the line is not the important thing because the essential factor determining the movements of the ball is the gradient of activity and strength in the line of players. Similarly, physicians sometimes think that because there is stagnation in a loop of bowel there must be mechanical obstruction ahead of it. This is not necessarily the case. If the men in the simile were to play in a lane between two board fences, a slowing of the progress of the ball would not mean necessarily that the lane had been narrowed or closed. As likely as not some of the players might be fighting back too hard or those above might not be pushing down as energetically as usual.

Some may be surprised at the idea of one part of the bowel resisting the propulsive efforts of another part above, but this phenomenon has been observed by so many people besides myself that I feel no doubt about it.

Dietary Suggestions. Some may ask: In what way can the idea of a gradient altered by disease influence our methods of treatment? The answer is that so far little has been done because therapists have not been thinking along these lines. Later we may be able to get drugs which will help in restoring the normal gradient, perhaps as calomel does, but without unpleasant by-effects. In the meantime there is a diet which is very helpful, probably because it does not lead to conflicts with disordered gradients. Years ago I became impressed with the fact that many of the patients who complained of flatulence and intestinal unrest were passing stools which were full of lumps and undigested material, consisting mainly of cellulose. I found, also, that if I could remove much of this cellulose from their diets they would often get great relief, and the digestion of starches, as shown by the stool examination, would greatly improve.

It seemed to me then that the virtues of the smooth diet were to be ascribed mainly to its freedom from a substance—cellulose—for the solution of which the body has no ferment; but in recent years it has occurred to me that this diet might give relief to the digestive tract in still another

way. Remembering the experiment described in Chapter VII in which reversed segments of small intestine were shown to transmit fluids but not solids, it seemed to me that a person with a good steep gradient might be able to handle any amount of coarse and indigestible material, while a person with a poor gradient or one that is somewhat upset in places would be unable to do so. One so handicapped should avoid eating coarse food for much the same reason that he should avoid putting paper, sticks and cotton down a drain which has a poor drop and several narrow bends. At any rate, whatever the reason, this diet has certainly proved in actual practice to be of great value whenever there is a slight tendency to reverse peristalsis or to a narrowing of the lumen of the bowel. Thus it is useful postoperatively when suture lines or segments of bowel are still irritable; and it is absolutely essential in the presence of moderate intestinal obstruction such as occurs with carcinoma of the bowel.

What follows is a list of instructions such as for years I have had mimeographed to hand to patients:

THE SMOOTH DIET

This diet is based not only on practical experience, but on a number of scientific principles. We have no ferment in our digestive tracts to dissolve cellulose, that is, the fibrous part of vegetables and fruits. Most of this material is quite indigestible, and if we eat much of it we throw a heavy burden on the bowel. This fiber interferes with the digestion of starches and predisposes to flatulence.

If there happen to be narrow or irritated places in the bowel, or kinks and adhesions, the fiber may cause clogging and back pressure. The ideal diet in such conditions is one which leaves only a small liquid residue which can trickle past the obstructions; in this way it will often give prompt relief. This smooth diet is indicated also when the bowel is irritated, overly active, and responsive to every stimulus.

It should be tried out faithfully at first and then if it works well, other foods may be experimented with, one at a time. You may have learned by experience that some of the foods allowed on this list are hurtful to you; in that case leave them alone.

If you are to give this diet a fair trial, eat no coarse foods with fiber, skins, seeds, or gristle. Avoid particularly salads with celery, tomatoes, cucumbers and pineapple, many of the green vegetables, raisins, berries, jams full of seeds, nuts, and many of the raw fruits. Beans, cabbage, onions, green or red peppers, melons, cucumbers, and peanuts are notoriously gassy. If you are

living in a boarding house you can stick to this diet by simply avoiding the forbidden foods and eating more of the digestible ones which are put before you.

Avoid sugar in concentrated form and take no candy or other food between meals. Hot cakes and waffles might not be bad if they were not eaten with so much syrup. Fried foods are not bad if they are properly fried, that is, totally immersed in fat at the right temperature. Avoid eating when in a rush and when mentally upset. Family rows should take place away from the table. Chewing gum may cause distress, as much air is swallowed with the saliva. Digestion is greatly helped by a good chewing surface. If there are any gaps in your teeth have your dentist fill them with bridges. Purgatives often cause flatulence and distress in the abdomen.

The following are suggestions for breakfast: orange juice, grapefruit (avoid the fiber in the compartments): cantaloupe and melons are inadvisable. Coffee, if desired, is allowed in moderation; it sometimes causes flatulence. If you are sensitive to caffein try kaffee hag or instant postum, chocolate, cocoa, or tea. One or two eggs with ham or bacon (avoid the tougher part of the bacon), white bread, toast or zwieback with butter, any smooth mush such as farina, germea, cream of wheat, cornmeal or rolled oats,* puffed cereals, and cornflakes are allowed. Shredded wheat biscuits and other coarse breakfast foods are not allowed. Bran is particularly harmful. Graham bread is permitted but not the coarser whole wheat bread.

Suggestions for lunch and dinner: In fruit cocktails avoid the pieces of orange and pineapple. Broths, bouillon, cream soups, and chowder are allowed, also meat, fish or chicken, squab or game, excepting duck. Veal may be tried; it is not digested well by many persons. Eat no smoked fish or pork. Crab and lobster had better be left alone. Oysters and sausage may be tried later.

Bread and butter are allowed, and hot biscuits if they are made small so as to consist mainly of crust. Rice, potatoes, baked, mashed, hashed brown, or French fried, are allowed and later there may be added sweet potatoes, hominy, tomatoes stewed, strained and thickened with cracker or bread crumbs, well-cooked cauliflower tops with cream sauce, asparagus tips, Brussels sprouts, squash, beets, turnips, creamed spinach, Italian pastes, noodles, macaroni and spaghetti cooked soft, purées of peas, beans, lentils, lima beans or artichoke hearts. All skins or fiber should be removed by passing the food through a ricer. Sweet corn may be used if passed through a colander. There are practically no other vegetables that can be puréed to advantage. String beans† are allowed if they are young and tender.

No salad should be taken at first. Later you may try a little tender lettuce with apples or bananas, tomato jelly or boiled eggs. Mayonnaise and French dressing are allowed. Potato salad without much onion may be tried.

Suggestions for dessert are: simple puddings, custards, ice cream, jello, plain cake, canned or stewed fruits, particularly pears and peaches. Cottage cheese is permissible; other cheeses often cause trouble. Apple, peach, apricot, custard, and lemon cream pie may be tried if only the filling is eaten.

* A fine oatmeal can be obtained by calling for Robinson's Scotch Groats.

† Large, tender string beans which can be used as a vegetable or a salad can now be obtained in cans.

In case of constipation, stewed fruit may be taken once or twice a day. In winter the dried, pared fruit may be used for stewing. Prunes are probably the most laxative of fruits and if eaten every other morning they will relieve the average case of constipation. They should be cooked slowly until they almost go to pieces. If the skins are still tough they should be discarded. Apple sauce is much more palatable if made from unpared and uncored apples. The sauce is strained later. It may be mixed with a little tapioca or sago. The apples may be baked. (Apples, even when cooked, often cause distress.) Blackberries and loganberries can be stewed and strained and the sweetened juice thickened with cornstarch. This makes a delicious dish with the full flavor of the berries. Later you may try fully ripe pears and peaches.

Make no effort to drink water. Be guided by your thirst. Avoid excessive use of salt or other seasoning. If you wish to gain in weight eat as much cream, butter, fat, and starch as you can. If you wish to lose or to stay thin, live largely on vegetables, fruits, and salads, with a moderate amount of lean meat.

CHAPTER XXV

REVERSE PERISTALSIS AND ITS SYMPTOMS

It can easily be shown that most of the symptoms of gastro-intestinal disease are due to disturbances in the mechanical functions. Thus, the great obstacle to the making of an early diagnosis of cancer of the stomach is the fact that the mucous membrane and the gastric secretion may be almost entirely gone and yet the patient may have few symptoms of indigestion. These arise when the growth becomes large enough to block the pylorus, and even after that, they may disappear entirely when a channel sloughs through the tumor. As Taylor has aptly said, we seem to have duplicate plants for chemical digestion, but we have only one muscular tube for the motor transport of food. Naturally, when that breaks down we are very promptly apprised of the fact. As we undoubtedly get symptoms when the transport is slowed or stopped, it seems to me that we must get them also when it is reversed. I might add that we get very definite sensations also when the transport is speeded up. In a sensitive person the peristaltic rushes which usher in an attack of diarrhea may be very distressing. They produce a peculiar sinking feeling in the epigastrium which may be accompanied by chills, cold sweats, pallor of the skin, and even fainting.

Now it has been shown in the preceding chapter that the reverse transport of food in the tract is not uncommon: in some places it is physiologic. We know that the duodenal contents regurgitate into the stomach. We know that there is reverse peristalsis in the upper half of the colon; and all of us are acquainted with the phenomena of belching, regurgitation and vomiting. Since the time of Hippocrates, physicians have commented upon the fecal vomiting of ileus; and there are many well authenticated instances in which people have vomited enemas and suppositories (Schloffer, Langmann, Weber). A review of the literature shows a surprising number of cases in which these observa-

tions caused surgeons to operate for a gastrocolic fistula which was not found (Treves). I have talked with a number of intelligent persons who objected to their nutrient enemas because they were regurgitating some of the material, and did not like its bitter taste. Dr. Emge of San Francisco tells me that after severe pelvic operations it is his custom to give enemas of coffee which not infrequently can be detected in the vomited material. At first he thought it was dark blood, but a chemical examination showed that it was coffee.

It is well known that in most instances barium enemas flow back into the ileum and that occasionally the material will reach the duodenum (Quimby, p. 403). I have seen liquid and gas pass rapidly from the colon to the duodenum in cats. The animals were anesthetized and their abdomens opened under salt solution; the rectum was tied off and the colon filled with air or thick soup. After that part of the bowel had become very irritable and highly tonic through its efforts at emptying, some of the material was rushed well up into the small intestine.

Granting, then, that the possibility of reverse transport of food through the tract is well established, the next question is: Are there mild forms in which perhaps the gradient is simply flattened, or in which there are ripples traveling up the bowel, and do these ripples cause symptoms? Do they affect the consciousness of the individual, and if so, how? In the following paragraphs I wish to discuss a few symptoms which are often found together or alternating one with the other in the same patient, and which I believe indicate such mild reverse peristalsis. These symptoms are vomiting, regurgitation, heartburn, belching, nausea, so-called biliousness, coated tongue, some types of foul breath, a feeling of fullness immediately after beginning a meal, globus, and possibly at times, hiccup (Alvarez, 1917[c]). In taking a history, these symptoms should be inquired into very carefully, because if the patient has a lesion anywhere along his tract sufficiently irritable to alter the gradient, he should have some of these manifestations. If, on the other hand, he complains only of a little flatulence with some discomfort

or vague pain one must be slow to make the diagnosis of an organic lesion.

Vomiting. In Chapter xxiii will be found an account of a number of observations which show that the act of vomiting is often preceded by an increase in the activity of the bowel and sometimes by actual reverse peristalsis there. We are probably justified, therefore, in including vomiting in the syndrome of reverse peristalsis.

Regurgitation. In true vomiting, the return of the gastric contents into the mouth is effected mainly by contractions of the voluntary muscles in the abdomen and thorax; in regurgitation, it is effected mainly or solely by contractions in the smooth muscle of the stomach, bowel and esophagus. There are, however, many grades or stages between the two—between the projectile vomiting in cases of brain tumor, and the half vomiting, half regurgitation often seen in infants and in hysterical girls. Furthermore, a woman with, let us say, an irritable gallbladder may regurgitate during some of her attacks and vomit in others.

Regurgitation is commonly observed even in persons with good digestion, if they eat certain foods like onions, muskmelons, bananas or fats. They can taste these foods at intervals for hours after they are eaten. The fats probably act in this way because while they depress the activity of the stomach (von Tabora, Cannon, 1907, p. 315), they stimulate that of the bowel, and thus increase the normal tendency to duodenal regurgitation (Babkin, 1917; Lintvareff). It has often struck me as suggestive that those foods that cause regurgitation when eaten in small amounts may cause vomiting when eaten in large amounts. Furthermore, some of them produce heartburn in some people; and we shall see later that that is due probably to regurgitation of gastric juice into the pharynx.

Some women regurgitate at the beginning of the menstrual period; others have a great deal of trouble with it during pregnancy. The fact that regurgitation sometimes ceases a few minutes after the patient has a bowel movement suggests strongly that the distention of the pelvic colon can

keep that region overactive and can cause it to give off reverse waves. These waves need not be so powerful that they sweep material along before them. I have commented elsewhere on the fact that in the rabbit's intestine peristaltic rushes here and there can be shown by graphic records to have originated in ripples which have come, unnoticed by the naked eye, all the way from the pylorus (Alvarez, 1915[a]). It seems to me probable, therefore, that ripples coming from a full or overactive colon, or from the irritable ileocecal region in subacute appendicitis can run up the bowel and show themselves in the stomach and esophagus as waves of acid regurgitation. Smith and Lewald (p. 271) have commented upon the frequency with which regurgitation accompanies colic in children. It is probable that the waves causing this regurgitation arise in the overactive part of the bowel. The following case is very suggestive: A constipated infant regurgitated so much every day that her pillow was always soaked. After weeks of this her bowels suddenly became a little loose, and the day on which this occurred the mother was surprised to find the pillow perfectly dry. It remained that way for over a week until the bowels became constipated again. Apparently the establishment of a good current downward instantly stopped all regurgitation upward. Hippocrates seems to have had very similar ideas about the gradient, because he says: "In confirmed diarrhea, vomiting, when it comes on spontaneously, removes the diarrhea." I have seen exactly that thing happen in cases of tuberculosis of the cecum.

Heartburn. Before giving my views as to what heartburn is I must emphasize what it is not. Practically every one who has studied the subject has agreed that only a small proportion of the patients complaining of sour stomach or heartburn have an actual increase in gastric acidity (Schütz, Steele). Titration of the burning fluid that has been regurgitated often shows subacidity; and gastric analyses made during the periods of discomfort do not show values any higher than those found during periods of relief. Furthermore, as was seen in Chapter xiv, all of those who have put from 0.5 to 1.0 per cent hydrochloric acid by tube into the

normal human stomach agree that their subjects could hardly perceive it.

Several other explanations for the appearance of heartburn have been offered, but it seems to me the best one is that given by Reichmann, who in 1884 persuaded some volunteers to swallow a little gelatin-coated sponge on the end of a string. After leaving it for ten minutes in the lower esophagus he pulled it out, squeezed it, and found that the fluid expressed was acid in the persons who had heartburn and alkaline in normal controls. He concluded, therefore, that heartburn was due to a regurgitation of gastric juice. This view has been held independently by a number of men, but some doubt has been cast on it by the work of Hurst (1911, p. 12), who states that the esophagus is not sensitive to acid. This may be true of the middle and lower parts of the tube, but more study is needed on the sensitiveness of the upper part near the pharynx. Certainly some patients, when they have to take therapeutic doses of dilute acid, complain of burning somewhere in the pharynx or esophagus and I experienced severe burning once after drinking a solution of betain hydrochlorid; so far as I could tell, it was in the esophagus.

Recently Payne and Poulton brought forward evidence to show that heartburn is due to tonic contractions of the esophagus. I am inclined to think that they also are right and that under one heading we are really dealing with two somewhat different conditions. Not only are we as physicians vague about what we mean by heartburn, but our patients are even more uncertain. I suspect that sometimes they are telling us about waterbrash or acid regurgitation, in which the burning feeling is pretty definitely at the upper end of the esophagus, and at other times they are complaining about a peculiar burning or tearing feeling which seems to be located around the cardia. In either case I think the sensation is due primarily to the spreading upward along the esophagus of abnormal waves of contraction, which have arisen probably in the fundus of the stomach.

Some intelligent persons who have suffered greatly from heartburn have told me that their dentists have found the enamel badly eaten off their back teeth; and I believe some-

one has suggested that regurgitation of acid juice may be one of the causes for that deterioration of the teeth which is so often seen in pregnant women.

Some nervous women complain at times of a burning feeling in the epigastrium, as if the stomach were "on fire." This seems to be quite different from heartburn. The fact that it sometimes moves to the lower part of the abdomen or down to the thigh shows that it is a paresthesia which has nothing to do with the stomach.

One of the most suggestive things about one form of heartburn is its well-known association with belching and regurgitation. Many say that they feel the burning only when the fluid comes up. Occasionally it is worse when they are lying down, perhaps because the gastric juice can then more easily run back up the esophagus. It is often brought on by eating fats which, as is well known, tend to regurgitate. Some men suffer from heartburn after using tobacco. Perhaps in the habitué, regurgitation of gastric juice takes the place of the nausea and vomiting of the neophyte. Similarly, in a few sensitive individuals small doses of digitalis cause heartburn, whereas, as is well known, in large doses it produces vomiting.

If persons with heartburn ordinarily have no increase of gastric acidity, why are they so often relieved temporarily by the taking of alkalies? It seems to me that alkalies must be effective in several ways: First, by neutralizing the acid in the stomach; second, by enabling the person to belch so noisily and satisfactorily that he does not feel like doing it again for some time; and third, perhaps, by quieting the contractions of the stomach.

If heartburn is due to regurgitation of gastric contents into the esophagus, why is it that the fluid that comes up sometimes tastes fresh and sweet while at other times, in the same person, it is intensely acid and bitter? It is now well known that there are three parts of the stomach: (1) the fundus, which holds the food fairly motionless, often in layers as it comes in; (2) the muscular antrum, which breaks the food up and mixes it with the gastric juice; and (3) the canalis gastricus which carries fluids along the lesser curva-

ture and out into the duodenum. It seems to me that the regurgitated food that tastes fresh has probably come from the top of the pile in the fundus, the burning liquid has come from the antrum or even from the duodenum, and has probably traveled up the gastric canal. Schilling found that the regurgitated fluid was alkaline in some people; and in one case he thought it was pure duodenal juice.

Heartburn is often severe and trying in pregnancy where it may take the place of vomiting. Some women will suffer with vomiting in one pregnancy and severe heartburn in another. It is present sometimes on the first day of menstruation, and it may be a pronounced symptom in chronic appendicitis, in duodenal ulcer, and in gallbladder disease. In the last three conditions I think it represents reverse peristalsis arising near the lesion.

Belching. As is pointed out in Chapter xxvi, there are probably three types of belching: (1) a gurgling sensation or sound which seems to run up the esophagus, and perhaps out along the eustachian tubes; (2) an involuntary regurgitation of gas from the stomach; and (3) a voluntary swallowing and expulsion of air. This air ordinarily descends only into the middle or lower esophagus, but occasionally some of it is forced into the stomach (Kantor). I often tell these people that they are simply scratching themselves with the air. Often, as with scratching, the more the victim does the more he wants to do, so that the quickest way in which to get relief is to desist until the desire has passed off.

Although many of these patients are neurotic and are suffering from a bad habit, I believe that many of them actually have some organic lesion which is sending off reverse waves, is making them uncomfortable, and is giving them the desire to belch. It is remarkable the amount of relief that they get sometimes by taking a little sodium bicarbonate. A man will wake up about two in the morning with great distress; for an hour he may walk the floor, rubbing his abdomen and trying to belch. Finally, after taking some soda, he belches noisily; perhaps he vomits a little bile and water, and within a few minutes he is comfortable and falling asleep. The relief obtained is so out of

proportion to the amount of air or liquid expelled that it seems to me it must be due to a quieting down of the tract after the reverse waves have succeeded in running out. I can only compare it to the tremendous mental and physical relief that comes to a sensitive person when he reaches the toilet after he has restrained a rectum full of gas for hours at some public gathering. The violent peristaltic contractions cease instantly and the whole nervous system quiets down.

NAUSEA. Many years ago I (Alvarez, 1917[c]) suggested that nausea, perhaps not infrequently, has its origin in reverse peristalsis in the bowel, and since then a number of observations substantiating that view have been made by several men, among whom I may mention Wheelon (1921, 1923, and 1926), Keeton, Fitzgibbon, and Lehman and Gibson. It is suggestive that in 2 patients whom I saw with paralytic ileus developing immediately after operation there was no postanesthetic nausea or vomiting, but it is possible that there was something wrong with the vomiting center as well as with peristalsis.

Nausea is ordinarily not produced by lesions of the stomach alone because it is often entirely absent with extensive carcinomas of that organ, and it is not a prominent symptom of ulcer. It is much more common in acute and subacute appendicitis and other inflammations of the lower bowel. As is well known, it is very severe in pregnancy and occasionally it is seen with other disturbances of the pelvic organs. It is often marked in hysterical women who show other signs of reverse peristalsis. More rarely, it is observed in men with large prostates and distended bladders. I have seen it as the first and for months the only symptom of carcinoma of the colon but I have never seen it with esophageal disease or with regurgitation due to cardiospasm. Dogs appear to be nauseated when irritant solutions are injected through fistulas into the upper bowel, and we know that these substances regurgitate into the stomach (Cohnheim and Dreyfus, 1908[a], p. 2484). It is seen sometimes with cholecystitis, and Ivy has shown that it can be produced by distending the gallbladder or the ducts.

Patients suffering from nausea sometimes describe it as coming in ascending waves, and I have noticed the same thing myself. It has made me wonder if possibly I was feeling actual reverse waves in the bowel. When I am nauseated, the distress is lessened by lying on the right side and is made much worse by lying on the left. Other people have told me the same thing; but some think their nausea is worse when they lie on the right. These observations suggest that the sensation is affected by the position of the gastric contents. Nausea may be produced also by pulling on the mesentery during abdominal operations under local anesthesia (Farr), and Barclay (1910) believes that it is associated in man with a drop in gastric tone.

The nausea caused by disgusting mental impressions, by rolling movements, as at sea, and by cerebral and aural disease, might conceivably be due to a reversal of the gradient in the upper part of the tract, brought about by an unequal or dissimilar action of the vagus on different parts of the stomach and bowel. This possibility has been discussed in Chapter XXIII. It is an interesting point that in many cases of vomiting due to brain lesions there is no preliminary nausea. This observation agrees with the others in suggesting that the sensation of nausea is produced in the bowel and not in the brain. If this reasoning is valid, it can be used as an argument in favor of the view that some emetics tend to reverse the gradient in the bowel because, in small doses, they produce nausea without vomiting. It would be an interesting experiment to see whether persons whose vagi have been cut across, as in complete gastric resection, can experience nausea after taking emetics, or during spontaneous vomiting.

Some persons experience nausea when constipated and are relieved immediately after emptying the rectum; others are nauseated after taking enemas, particularly if those enemas contain irritant substances, and others feel nauseated when they are hungry, and get relief immediately after taking food. That probably restores the downward gradient.

Coated Tongue and Foul Breath. It is commonly supposed that the tongue in some sympathetic way reflects

the condition of the gastric mucous membrane, but I can find no proof for this view. It seems to be based on the idea that many gastrointestinal upsets are due to, or associated with, a gastritis. The recent more careful study of stomachs which have been filled with formalin solution immediately after death, and the work done on sections removed at operation have shown that gastritis is a rather rare disease (Beitzke). About the only place in which it is found is in the neighborhood of large gastric ulcers, carcinomatous and benign. It would seem now to be a poor diagnosis to make even in alcoholics, since Hirsch (1916) has shown that true inflammatory changes are hard to demonstrate in the stomachs of patients dying from delirium tremens.

By far the best explanation for the coated tongue has been given by Kast. He gave lycopodium powder in sealed capsules to a number of persons, and was able to recover the typical spores in the mouths of most of them the next morning. I have had no difficulty in confirming these experiments. In one case, that of a woman who regurgitates a good deal, particularly during the menstrual period, the tongue became yellow from the lycopodium.

It is possible that some of the particles making up the coat of the tongue may come even from the bowel; and Grützner (1894, 1898) and others (Swiezynski, Reach, 1902, Bernheim) have reported experiments that suggest that lycopodium spores or other finely divided and easily recognizable material given in enemas can travel in a few hours from the rectum to the stomach. Actually they were not always careful enough about excluding the possibility of the animal's having licked its anus or eaten its feces; so that much of this work is valueless. Uffenheimer however, and Dieterlen and others did, I think, exclude the possibility of such contamination and still saw reverse transport of material; and one of my students told me that he washed lycopodium spores out of the stomach of a man who the night before, was given a small enema containing the powder.

These observations do not surprise me because I know how far liquids can seep through the bowel. In cases of pelvic peritonitis with intestinal obstruction, I have seen a brown

coating on the tongue with a typical fecal odor long before fecal vomiting appeared. Hence it seems to me probable that many of the coated tongues which we see are due to the regurgitation of gastric and intestinal contents, especially during the night. This view is strengthened by the fact that the coating is often heaviest at those times when belching, regurgitation and a feeling of "biliousness" are most pronounced. Rather against the idea that bacteria and other small bodies travel up the bowel from the colon is the observation of Torrey and others that at different levels of the small intestine there are different flora which maintain themselves fairly constant. Perhaps, however, it is no more strange that this zoning of bacterial types should be maintained in the face of ascending contaminants than that it should be maintained in the face of descending ones.

It is commonly assumed by both laymen and physicians that the bad breath, coated tongue and bad taste in the mouth associated with constipation are due to the exhalation of absorbed toxins which have come through the blood. I have given elsewhere my reasons for putting little faith in these theories of autointoxication (Alvarez, 1919[a]). The bad breath of patients with diabetes and nephritis, or of persons who are dying may be due to exhaled substances, but I think the mechanism is quite different in constipation. There it seems more probable that the odor comes from gastric or intestinal material deposited on the back of the tongue. I need hardly say that the reverse currents must not be blamed for every coated tongue. There are other factors often present in the nose, mouth, pharynx and salivary glands which must be studied in individual cases.

Feeling of Fullness after Beginning to Eat. In rare cases this may be due to an actual shrinkage in the capacity of the stomach due usually to syphilitic ulceration, but ordinarily the roentgen-ray examination shows a normal or even a dilated stomach. Sometimes the patient ascribes his feeling of fullness to the presence of gas, but again, a careful examination often shows that he is mistaken. Carlson (1916, p. 111) has shown moreover, that these sensations do not arise in the gastric mucous membrane.

Hurst (1911, pp. 22 and 28) found that they may arise if the intestine is distended too rapidly by food coming through a gastroenterostomy opening; and I have seen the same thing during jejunal feeding.

It seems to me suggestive that these sensations are often associated with other signs of back pressure. Sometimes this pressure is so strong that the patient can hardly swallow. He says that the food does not seem to want to go down, or that he feels as if something met it and pushed it back. That apparently is one of nature's methods of telling us that the gradient is reversed and that the tract is not prepared to receive food. The intensity of this feeling in some persons may be seen from the following case history:

Two healthy boys, seven and eight years of age, respectively, ate heartily of blackberries at dinner. The next morning the younger one had diarrhea, but the elder seemed all right. Early in the afternoon, however, he began to complain of dizziness, a queer feeling of pressure in his pharynx, and recurrent waves of nausea which came every twenty or thirty minutes. Once or twice he retched unsuccessfully. Between the attacks of nausea he played happily. At supper time he made several attempts to eat, but each time said the food would not go down; something seemed to push it back. He then felt like defecating and with the help of an enema passed a hard plug of feces. Shortly afterward came a large soft movement containing the remains of the blackberries, and immediately after that he asked for food. He then found he could eat a large meal without any difficulty.

This child appears then to have had a series of reverse waves which arose in a colon distended by irritant material. These waves were perceived by him as surges of nausea and dizziness, as a tension in the throat, and an inability to swallow. The upset in the gradient was such that the tract would not accept food. Although these sensations were very definite so far as the child was concerned, it might have been impossible to show much change with the roentgen ray beyond, perhaps, a gastric stasis. If, however, the lower bowel had not been emptied when it was, he probably would have vomited large amounts of intestinal fluid next

day, and a few days later the material might have been fecal in character. There would then have been no doubt about the existence of reverse peristalsis.

This case brings up still another point, and that is that we can probably study reversals of peristalsis more satisfactorily in children than in adults. The intestine in children is short, its various parts are functionally knit together, it is very sensitive, and its gradient is easily reversed. Hence it is, perhaps, that organic lesions often produce just those symptoms that are to be expected from the gradient theory. In adults, various complicating factors may enter to obscure the picture.

Globus. A few times in my life I have happened to swallow while a wave of regurgitation was on its way up the esophagus, and when the two waves met there was a painful tearing feeling. It may be that globus is brought about somewhat in that way (M. Hall). Some patients describe it as a lump moving up and down the esophagus, and it is suggestive that the hysterical, who are supposed to suffer most from globus, sometimes present the most striking manifestations of reverse peristalsis.

Hiccup. There is no doubt that under certain conditions of diaphragmatic irritability, involuntary belchings of gas or waves of esophageal regurgitation will be followed immediately by a spasmodic contraction of hiccup. Similar contractions will sometimes be excited by swallowing, particularly with hot fluids. In these cases it seems likely that the diaphragm is stimulated either by a sudden distention of the fibers around the esophageal opening, by the sudden warming, or by the action current of the esophageal muscle. The last mentioned theory seems not improbable because the diaphragm has been observed to twitch rhythmically under the stimulus of the action current of the heart. It is suggestive that hiccup is not infrequently a troublesome symptom after serious operations when the gastrointestinal current is plainly reversed. Other factors are undoubtedly at work, and there probably are many varieties of hiccup in which reverse peristalsis plays no part.

"BILIOUSNESS." This is often nothing more than the layman's term for the reverse peristalsis syndrome. Certainly, few thinking physicians today would ascribe that group of symptoms to hepatic insufficiency, although they are often seen with definite gallbladder disease. More often the reverse waves seem to be due purely to the stagnation of the colonic contents in constipation. Biliousness derives its name probably from the fact that the sufferers note bile in the regurgitated or vomited material. Since the presence of bile in the stomach is normal, any excess found there need not indicate disease of the liver but only an increase in the normal duodenal regurgitation. Many of these patients are found at operation to have actual organic disease like cholecystitis or chronic appendicitis; others, whose attacks are ushered in by violent headaches have, I believe, a hereditary brain disease; a sort of sensory epilepsy. Some irritable area in the brain seems to send down the vagus a "storm" which upsets the intestinal gradient much as it is upset in seasickness or Ménière's disease. In a number of cases I have seen the severity of the symptoms and perhaps the number of attacks diminished after the removal of a diseased gallbladder or appendix, but a little fatigue could still bring on a typical headache.

The relief which these people derive from purgation, and particularly purgation by calomel, is due not to any action on the liver (for all pharmacologists are agreed that there is no cholagogue action), but, I believe, to a restoration of the downward current. The relief comes so promptly after the evacuation of the bowel that I am sure it cannot be due to the removal of a source of toxins (Alvarez, 1919[a], p. 12). If the symptoms were due to circulating poisons they would have to wear off gradually like those of an alcoholic debauch.

Those who may feel that I have appropriated too many of the gastrointestinal symptoms for this syndrome should remember what I said at the beginning of this chapter. If, as seems likely, symptoms are produced almost entirely by disturbances in motor functions, we should be most conscious of, and most annoyed by, the severest possible form of such disturbance, namely, a reversal of the current.

In other words, many or most of the sensations that reach the brain when digestion is disturbed should be those originating in reverse peristalsis.

Difficulties and Objections. The question that will probably arise in the minds of many is: If reverse peristalsis is so common, why do we not see more of it with the roentgen ray? It seems to me that there are several answers to this question. In the first place, it must be remembered that we generally screen patients during intervals when they are not acutely ill and are not showing many symptoms. If we could watch the movements of the bowel in the acute stages of appendicitis, in acute ileus, or during the first two or three days after intra-abdominal operations, we should probably see enough reverse peristalsis. Actually we do see, not infrequently, reverse waves in the duodenum, and on rare occasions I have seen them in the terminal ileum. Unfortunately, the food goes so rapidly through the jejunum and upper ileum that we can seldom see what is going on there.

It must be remembered also that many of the disturbances seem to be due to ripples which are not deep enough to force the barium along the bowel. As I have shown in Chapter xviii, there is no doubt that a small peristaltic rush in the lower ileum, or a wave that forces material through the ileocecal sphincter, is often part of a ripple that has come from the duodenum. One might not suspect it if it were not shown so clearly on the records obtained with six or seven enterographs, recording simultaneously. These ripples do not move the material in the bowel unless they break into peristaltic rushes or into defecating movements in the colon. They are like the waves of the ocean which do not carry a boat with them for any distance unless they are breaking on a shelving beach. Similarly, in the digestive tract, ripples in the orad direction breaking into waves at the cardia probably cause many of the symptoms of indigestion.

Another point to be remembered is that animal experiments suggest that the basic gradient may be more nearly flattened or reversed in one segment of the tract than in another, so that there may be reverse waves in the stomach and normal ones in the intestine. That would tend to com-

plicate the problem. To my mind, the best answer to be made to those who cannot accept the idea of reverse peristalsis until they see more of it with the roentgen ray is that if they wait for that, they will fail to recognize what is going on in the milder, more common disturbances. Similarly, if they wait to diagnose gallbladder disease until the patient has colic, jaundice and demonstrable stones, they will miss perhaps 95 per cent of the early cases. It seems reasonable to suppose that the brain of a sensitive person should detect, or in some way become conscious of, abnormalities in peristalsis long before they are severe enough to become visible on the roentgen-ray screen. Furthermore, these disturbances are often so transient that it would be hard to demonstrate them objectively.

Another question is: How can signs of reverse peristalsis appear from time to time during digestion, when food is actually going down the tract? This objection does not seem insuperable when we remember that waves can travel at the same time in different directions over one medium. Recently I stood on the banks of a stream which was flowing north. The wind was blowing hard enough to make wavelets traveling in the opposite direction. A passing launch produced other waves which came from the east and were reflected at the shore. Three types of waves could easily be identified going in three directions over water which was flowing in a fourth.

I think ripples can travel up and down the intestine in much the same way. They may, perhaps, skip regions in which the gradient is fairly normal to produce anastalsis in regions where it is reversed. It must be remembered also that liquids can be forced through portions of the tract in which the gradient is definitely reversed. This is shown by the experiments in which sections of bowel are cut, reversed, and anastomosed again. We know also that fluid introduced into the colon under pressure can be made to run out at the mouth. Moreover, liquids will go through stretches of bowel in which the muscle is paralyzed or from which it has actually been removed (Kreidl and A. Müller, A. Müller and Kondo). We need not think always of the food as going

with the gradient and the ripples against it, because in parts of the tract the ripples might conceivably be going with the gradient and the food against it. It must be remembered, of course, that this discussion is at present quite theoretical. There is some analogy, perhaps, in the heart, where the blood may continue to travel in the usual direction, although the electrocardiograph shows that the ventricle is contracting a fraction of a second ahead of the auricle.

Actually on many occasions both in man and in animals I have seen normal and reverse waves running over the stomach either at the same time or alternately. Sometimes waves appeared at about the middle and ran both ways, and sometimes waves descending from the cardia met waves ascending from the pylorus.

The difficulties that have bothered me most have been connected with the lack of absolute parallelism between the various gradients under certain conditions and in some parts of the tract. For instance, although asphyxia and KCN are supposed to affect the metabolic gradient in the same way, and although the tracings shown in Figures 88 and 89 are remarkably alike so far as amplitude of contraction is concerned, they are not alike as regards rhythmicity; KCN markedly slows the rate of contraction and asphyxia affects it little or not at all until it is stopped entirely. Moreover, asphyxia has little effect on the colon, while KCN depresses its activities. Theoretically, KCN should have less effect on the colon than on the ileum if the severity of the reaction is dependent solely upon the oxygen need of the tissue.

There are a number of such technical problems which await solution during the coming years, and the answers to them will undoubtedly modify some of my present views. Fortunately, however, the best discoveries often come through the solution of difficulties which at first seem most embarrassing and most disturbing.

CHAPTER XXVI

FLATULENCE

Flatulence is one of the commonest symptoms complained of by patients seeking relief from gastrointestinal disorders; it accounts for much of the distress and some of the danger that attends abdominal operations, and it is an annoying complication in a number of diseases. One would think that such an important condition would, in the course of time, have been well studied, but although some good work has recently been done on the problem, our knowledge is still highly deficient. The first thing needed to improve it is to collect, analyze, and render available such facts as are now scattered through technical journals; and that is what I shall attempt in this chapter.

WHERE DOES THE GAS COME FROM? In the first place, much of it is swallowed. There are many persons who, in their efforts to relieve themselves of an uncomfortable feeling about the cardia, learn to gulp down large mouthfuls of air. Fortunately, most of this air never gets past the cardia but is immediately eructed; occasionally, however, some does go on into the stomach. It may easily be that the desire to swallow is due, at least in part, to the patient's unconscious efforts to reverse and force downward ripples that are coming up the esophagus, and it may sometimes be due also to the salivation that accompanies disorders of the digestive tract. Some persons chew gum because they actually find that the repeated swallowing combats a tendency to regurgitation and nausea.

It is possible also that some flatulent persons whom we do not now recognize as air swallowers because they do not belch, have really some peculiarity in their mode of swallowing or perhaps of frothing the saliva which causes them to get more than the usual amount of air into the stomach. Cannon (1911[a], p. 165) showed on himself that it can easily be introduced with certain foods such as soufflés, light omelettes, and toast, and he also obtained some evidence to show that a

portion of this air, still mixed with the food, can go on into the bowel. Carnot (1907) also, in his fistula dogs, heard air passing through the pylorus toward the close of digestion. Kantor (1918) reports having seen air swallowers who were able so to fill their stomachs that some of the gas was passed on into the bowel; but my own impression after years of experience with the roentgenoscope is that such an occurrence must be rare and quite impossible with the subject in an upright position. It might happen, perhaps, with the subject lying on his left side, because the bubble could then get into the pars pylorica, and from there into the duodenum. It could happen more easily also in the steer-horn than in the fish-hook type of stomach.

Actually, McIver, Benedict, and Cline recently showed that this passage of air into the bowel probably takes place when patients are lying recumbent after operations, and that it has much to do with producing the discomfort and distention that are so commonly complained of. They have shown also that much of this distress can be circumvented if, before the patient returns to his room, the surgeon will only pass a stomach tube and remove the air.

The ease with which gases can get into the stomach, perhaps with swallowed saliva, was shown during the war, when, in many of the soldiers who were injured by mustard gas, severe gastritis and enteritis developed. It is possible, however, that some of the gas taken in by the lungs was excreted from the blood because some of these men had inflammation also of the lining of the gallbladder (Stenhouse).

It is hard to believe that much of the air that reaches the stomach goes on into the bowel because, at least in adults, the roentgen ray seldom shows much gas in the small intestine. When there are considerable amounts, it is because there is an obstruction in the small bowel. In animals, also, Schoen could seldom find any gas in the small bowel. We know that some air probably does pass through into the colon, because analyses of flatus have shown the presence of considerable amounts of nitrogen (Fries, Ruge). As will be seen later, some or all of that gas might be excreted from the blood into the lumen of the bowel, but I think the chances are

that a good deal of it represents the residue from swallowed air. When Yllpö injected large amounts of air into his stomach he had flatulence on account of the nitrogen which he could not absorb; when he used oxygen he had a little flatulence, and when he used carbon dioxid, he had none at all. An extensive review of the literature on swallowed air is given by Kantor.

An idea of the amount of nitrogen that normally reaches the anus can be gotten from the analyses of flatus made by Fries. He found in a healthy man that single discharges varied from 50 to 500 c.c., with an average of about 100 c.c. About a liter of gas was passed in a day. It was odorless, and burned with a slightly luminous flame. The percentage composition by volume was

CO_2	10.3
O_2	0.7
CH_4	29.6
N	59.4

Ruge's analyses showed percentages of nitrogen ranging from 10 to 64 per cent.

In man, in the erect position, the fundus of the stomach always contains a bubble of air which has been trapped there above the level of the cardia. This so-called *Gas-blase* usually contains about 50 c.c. Any excess is probably soon eructed, as shown by the fact that one can observe hundreds of patients with the fluoroscope before finding one with enough air in the stomach to excite remark. Some of them will complain that their stomachs are distended, but the examination will show that they are mistaken; in some the gas will be in the splenic flexure, and in others there will be no gas at all.

Infants seem to have more trouble from the gastric bubble than do adults, perhaps because in them it is larger in proportion to the size of the viscus, or because the stomach is more globular, or because they have to lie on the back so much of the time. The air gets trapped away from the cardiac opening, and they cannot get rid of it until some sensible person comes along and holds them upright for a few minutes.

In taking the histories of patients complaining of flatulence it is important always to find out whether they belch

or bloat or pass wind, because if they are only belching, their trouble may be due purely to air swallowing; there may be no increase in the production of intestinal gas, and it would then be foolish to order a change in diet. Such persons need first to break themselves of a bad habit; later they may have to part with a bad gallbladder, attend to an increase in blood pressure, or take a rest cure.

Fermentation of Food as a Source of Gas. It is questionable how much of the gas in flatulence is due to an increase in the amount of intestinal fermentation. Almost certainly the fermentation of the contents of the stomach has nothing to do with it. Such fermentation can occur only when ulcers or tumors have blocked the outlet of the pylorus and even then, with the roentgenoscope, we do not see much gas. Ordinarily the food goes through the stomach so rapidly, and the acid gastric juice and the swallowed oxygen so restrain the growth of bacteria that there is little chance for the formation of gas. Several investigators have shown also that even when gastric or intestinal contents are put away in an incubator they give off very little gas (Dunn and Thompson).

As Kantor has pointed out, many years ago, before it was customary to relieve marked degrees of gastric stasis surgically, there were persons who could amuse themselves and their friends by lighting the gases that emerged from their mouths. It all started when a man who was lighting his cigar happened to belch and discovered that the gas was inflammable. Similar observations have been made on flatus, which often contains enough methane and hydrogen to burn. According to Ruge the colonic gases of men on different types of diet have about the following composition:

	Milk diet		Meat diet			Diet of legumes		
			After 24 hrs.	After 48 hrs.	After 72 hrs.			
CO	16.8	9.0	13.6	12.5	8.5	34.0	38.4	21.0
CH_4	0.9	0.0	37.4	27.6	26.5	44.6	49.4	55.9
H_2	43.9	54.8	3.0	2.1	0.7	2.3	1.6	4.0
N	38.4	36.7	46.0	57.9	64.4	19.1	10.7	18.9

In the small bowel there is probably little or no fermentation or putrefaction because, at least in the jejunum, the chyme is fairly sterile and is traveling too rapidly toward the colon. The one place in which fermentation and putrefaction of food residues can be looked for is in the right half of the colon where there is the necessary combination of stagnation, fluidity of the culture medium, and abundance of bacteria. As will be seen later, even when fermentation is active, other factors must enter in before the patient can be annoyed by flatulence, because normally so much of the gas is promptly taken up by the blood and excreted by the lungs.

This method of excretion is particularly striking in the herbivores. Thus, Boycott and Damant found that goats produce in their roomy stomachs and ceca from 10 to 30 c.c. of hydrogen and methane per kg. per hour, so that an average goat of 20 kg. will in a day produce 9 liters. Fries found that a grown steer produces in a day from 100 to 250 liters of methane alone. The amounts of carbon dioxid evolved in the ceca of the herbivores and excreted through the lungs are so large and so hard to measure that they inject a considerable error into all calculations of the respiratory quotient.

Fries (1902) found that steers put out more methane when the proportion of hay in the diet is increased. He suspects that even in man, determinations of the respiratory quotient may at times be affected by the amounts of carbon dioxid coming from the bowel, but Dr. Boothby tells me that he thinks it improbable. In ruminants one-tenth or more of the carbon dioxid given off by the lung may come from the digestive tract. Although the rapidity of gas exchange in the bowel is remarkable it can easily be shown that it does not approach that which takes place in the lungs (Schoen).

Zuntz and Tacke concluded from their studies on the rabbit that in that animal also, from ten to twenty times as much intestinal gas is excreted through the lungs as is passed through the anus. An idea of the rate at which these gases are being carried off can be obtained by simply opening a rabbit under salt solution and noting that so long as the animal is alive the bowel gives off practically no odor, but

as soon as it is dead the stench from the cecum becomes annoying. Apparently the offensive element of the gas is removed, perhaps during its passage through the liver, because it is not noticeable on the breath of the rabbits. Extensive studies on the composition of the intestinal gases in animals have been made by Tappeiner.

That an absorption of gas from the bowel is constantly taking place can be shown also by tying the vessels running to or from a closed loop. Kader, Murphy and Brooks and others have shown that when this is done large amounts of

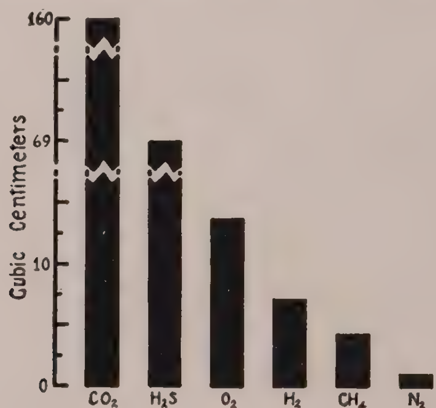

FIG. 92. Relative rates of absorption, expressed in cubic centimeters, of CO_2 H_2S, O_2, H_2, CH_4 and N_2 from a 25 cm. loop of small intestine. The height of the columns represents the number of cubic centimeters of the gas absorbed over a period of one hour.

gas pass backward from the blood into the lumen of the gut. It has been shown also that if loops of bowel are closed off and left in the animal they do not collect much gas, but if they are cut out and left in an incubator, they do.

Schoen (1925[b]) quotes Kato, who tied the portal vein in rabbits and found a greatly decreased absorption of CO_2, and Litten, who tied the superior mesenteric artery and obtained a great distention of the bowel. Schoen (1925[b]) closed off loops of colon in rabbits and obtained distention only when he at the same time interfered with the circulation. He found that in order to produce meteorism in the small bowel

he had to block its circulation much more completely than was necessary for the colon. This was because the small bowel absorbs gas so much more efficiently than does the colon, partly on account of its more corrugated surface and largely because its circulation is so much better. He either tied the mesenteric vein or narrowed the lumen of the portal vein and diminished the amount of absorption of gas in the bowel.

The amounts of carbon dioxid formed in the intestinal wall as a result of the activity of the muscle are too small to have much to do with the production of flatulence. Small amounts are formed in the stomach through the action of the hydrochloric acid on the carbonates of the food, and large amounts are probably formed in the duodenum through the neutralization of the carbonates of the pancreatic juice. Normally this gas is not likely to produce flatulence because, as will be seen later, it is almost immediately absorbed through the mucous membrane.

Excretion of Gas into the Bowel. For many years clinicians have been impressed with the fact that bloating often comes on so suddenly that it is hard to believe that it can be due to any known process of fermentation. Over a century age, we find John Hunter saying, "I am inclined to believe that the stomach has the power of forming air or letting it loose through the blood by a kind of secretion." Perhaps this mechanism is a relic of the one which our fishy ancestors used in their swim-bladders. As is well known, most fishes have an air bladder which helps them to maintain their position at different levels in the ocean; in a few species it has a connection with the outside of the body, but in most of them the gas is passed, as required, backward and forward through a special structure in the wall of the sac. The student who wishes an entrée into the literature on this interesting mechanism may consult an article by Hall. It might be noted also that one fish, the Cobitis fossilis, actually breathes with its digestive tract (Calugareanu).

One of the first to show the excretion of gases into the digestive tract of man was Schierbeck. His work, done on the stomachs of dogs, was confirmed later on normal human subjects by Woodyatt and Graham. They inflated the

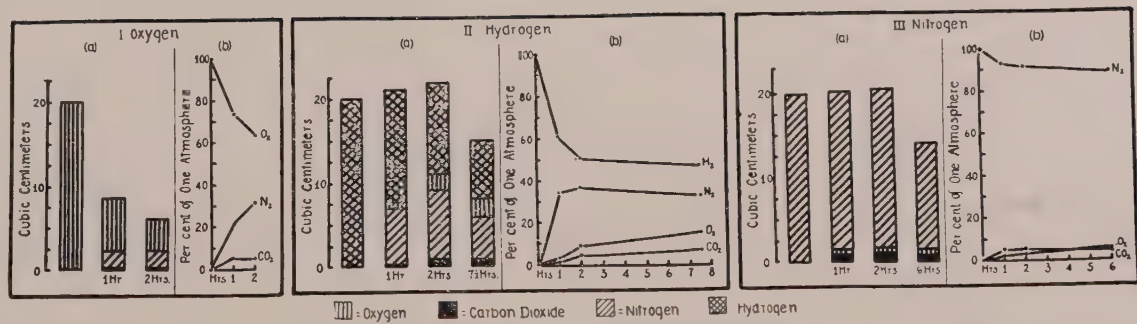

FIG. 93. The course of events following the introduction of (I) O_2, (II) H_2, and (III) N_2 into an isolated loop of small intestine. The gases were injected, allowed to remain for the period of time indicated, drawn off, and analyzed. The first column in diagram *a* represents in cubic centimeters the volume of gas injected; the succeeding columns represent the total volume of the gas and its composition when withdrawn from the intestinal loop after stated intervals of time. The percentage results of the analysis are plotted in diagram *b*. The line descending from the upper left corner indicates, in percentages, the absorption of the injected gas. The lines ascending from the lower left corner show the rate of entrance of the blood gases. (*From McIver, Redfield and Benedict.*)

stomach with gas, and five minutes later withdrew samples for analysis. They found always that a certain amount of carbon dioxid had been added to it. Sometimes the tension of this gas in the stomach was higher than that in the blood, suggesting strongly that active secretion had taken place.

All observers have noticed that there is a strong tendency toward the production of a balance between the tension of the various gases in the stomach or intestine, and the blood (Dunn and Dunn). When considerable amounts of any gas are injected into the stomach or bowel, the tension gradually drops until it approaches that of the tissues, and *pari passu*, the rate of its outward passage is slowed. Figure 93, taken from the excellent article of McIver, Redfield and Benedict, shows clearly what happens when small amounts of oxygen, hydrogen, or nitrogen are injected into loops of bowel. In every case some gas from the blood diffuses into the intestine as the injected gas goes out.

The large amounts of nitrogen that diffuse into the bowel are of interest because they do not readily pass backward again, and have therefore to be carried to the anus and expelled as flatus. This gas not only has a low diffusion constant but the blood and tissues are already too full of it to take up much more and the outside air is largely made up of it. As one would expect, when nitrogen is injected into a loop of bowel and the animal is made to breathe pure oxygen, there is a decided increase in the rate of disappearance of the nitrogen, as well as an increase in the rate of diffusion of oxygen into the loop (McIver et al.).

This excretion of gases from the blood into the stomach and intestine has been observed by Schoen, Dunn and Thompson, Kantor, Boycott, Yllpö, and others. Schierbeck's idea that carbon dioxid is secreted into the stomach *pari passu* with the hydrochloric acid has not been confirmed (Dunn and Thompson).

How Gas Gets Out of the Bowel. The passage of gas from the bowel into the blood and from thence to the outer air has already been touched on. There are a number of factors which determine the rates at which different gases pass through at different times, such as the diffusion con-

stants for the gases, their tendency to combine with hemoglobin, or to dissolve in the plasma of the blood; and the relative tensions of the gases in the intestine, in the tissues, in the blood, and in the outer air. Figure 92, from McIver, Redfield and Benedict, shows the rates at which the different gases escape from the intestine. Schoen (1925[a], p. 241) gives the following constants for the rate of diffusion and absorption of gases in blood at 38° C.

N_2	0.012
H_2	0.016
O_2	0.023
CO_2	0.540
C_2H_2	0.740

McIver and his coworkers anesthetized animals, opened their abdomens and gently tied off loops of bowel about 25 cm. long. They then injected 20 c.c. of gas, returned the loop to the abdomen for a while and later removed the remaining gas for analysis. When the stomach was used, the cardia and the pylorus were tied. As will be seen from the figure, carbon dioxid diffuses very rapidly, oxygen more slowly, and nitrogen hardly at all. Those who would like to learn more about the possible reasons for these differences should consult the original article. See also von Mering (p. 474), Boycott, and Schoen.

Hydrogen disulfid, oxygen and carbon dioxid disappear from the bowel more rapidly than one would expect from their diffusion coefficients, but that is due to the fact that they combine chemically with constituents of the blood. Nitrogen, on the other hand, leaves the bowel even more slowly than one would expect because the blood and tissues are already saturated with it. McIver and his associates found, as did Zuntz and Tacke, Boycott and Damant, Fries, and others, that the bowel can excrete through the lungs considerable quantities of hydrogen and methane.

It may be of interest to note that at one time in the past, an attempt was made to cure tuberculosis by injecting hydrogen disulfid into the colon. In spite of the fact that the

gas is decidedly poisonous, good results were, for a time, reported. (See Wood, Haggard, and Van der Willigen.) It is interesting to note also that satisfactory general anesthesia can be maintained by putting mixtures of ether and oil into the rectum. According to Schoen (1925[a]), acetylene will diffuse into or out of the bowel more rapidly even than CO_2.

It seems probable that in some cases bad breath is due to the absorption of evil-smelling gases from the bowel, especially as in rare instances a type of fecal odor peculiar to the individual can be recognized. Ordinarily, such gases are probably deodorized during their passage through the liver. An extensive study of the influence of the various intestinal gases on peristalsis has been made by Bokai (1887[b]). According to Ruge H_2S is found only in traces even in foul-smelling flatus. It is stated by some authorities that bismuth saves the bowel from irritation by combining with H_2S to make the black sulfid which is so often seen in stools.

CLINICAL APPLICATIONS

It appears, then, that gas is continually getting into the bowel and as continually being excreted through the blood and lungs. In the healthy person this process is so well balanced that there is no distress and practically no flatus. The next question is, how does this balance get upset, and how does flatulence arise?

The facts brought out in the foregoing discussion should make us look for flatulence in those conditions which lead to:

1. A greater swallowing of air.
2. A slowing or stoppage of the intestinal current.
3. An interference with the prompt digestion of carbohydrates.
4. An interference with intestinal absorption.
5. An interference with the intestinal circulation.
6. An interference with the gas-carrying powers of the blood.
7. An interference with exhalation from the lung.

A Greater Swallowing of Air. This topic was discussed at the beginning of this chapter and more can be found

about it in Chapter x. It is possible that the chewing of gum is responsible for the flatulence of some persons, but it is hard to be sure of this since many chew it because they feel that it relieves indigestion, and it is quite possible that it does so on account of its tendency to maintain the downward direction of peristalsis. It might be an excellent thing to prescribe postoperatively, not only to keep the mouth clean and the parotids active, but also to start up the desired peristalsis. Actually, some surgeons do use it in this way.

A Slowing or Stoppage of the Intestinal Current. This can cause trouble, not only through the failure to pass on the unabsorbed nitrogen, but through some other way not yet understood. I have often noticed that any interference with peristalsis is likely to be associated with the accumulation of large amounts of gas, much of which has probably come from the blood. Many sensitive persons with irritable colons dread formal dinners and public gatherings because they know that if a call of nature has to be deferred, the colon is likely to fill rapidly with gas. That it is not swallowed air coming from above is indicated by the fact that the minute the gas is expelled, perhaps with a small plug of feces, the vicious circle is broken, and the flatulence does not return. In many cases flatulence is probably the result of constipation and can be cured only if the bowels can be made to move fairly normally as with enemas of physiologic salt solution. Purgatives will apparently produce flatulence in sensitive persons, and gas is troublesome also in some cases of diarrhea.

An Interference with the Prompt Digestion of Carbohydrates. It is commonly stated that flatulence will occur if considerable amounts of undigested starch reach the colon where they can be attacked by bacteria. Although this may be true in some instances, the study of hundreds of stools has made me feel that there are a number of other factors involved in the problem. Large amounts of fermenting material can be found in the stools of avowedly healthy young men and women who do not complain of flatulence. Perhaps more important than the starch is the cellulose, for if the vegetable cells are not well broken up by cooking and masti-

cation, not only will there be a great deal of undigested starch in the stool, but the feces will be full of large masses of food, which interfere, not only with proper absorption, but with proper peristalsis. Physicians commonly remove starch from the diet of their flatulent patients and substitute cellulose which, in my experience, is much more harmful.

Some observations on a patient with a jejunal fistula have suggested one of the ways in which fresh bread may cause flatulence and indigestion (Lehman and Gibson). It was noticed that when toast was eaten, only a small amount of liquid material appeared at the fistula, but when soft bread was given, smooth, doughy lumps, sometimes as big as pullet's eggs, were passed. These not only were impossible of digestion but they served sometimes to produce cramplike contractions of the bowel. Flatulence is due often to the eating of rough indigestible foods and it comes also from eating beans, cabbage, peanuts, peppers, cucumbers and other foods which apparently have components irritating to the digestive tract.

It may be, also, that flatulence is due to the presence of abnormal types of intestinal flora or protozoal parasites, but as yet we know very little about the subject. Boycott and Damant and Schoen have even suggested that some of the oxygen formed in the intestines of herbivores is used up by bacteria.

An Interference with Intestinal Absorption. Dunn and Thompson think it not unlikely that some day flatulent persons will be shown to be defective in their ability to pass gases back and forth through the gastrointestinal wall. We are becoming more and more interested in the gas exchanges of the body cells and in the ways in which they take up and give off water, and it may be that before long we shall know something about the way in which the individual intestine can take up and give off gas.

Kato experimentally provoked inflammation of the mucous membrane of loops of bowel in animals and found that, if anything, the gas then departed a little faster; this agrees with the observations of Schoen (1925[b]). Kato, Kader, Schoen and others all agree that disturbances of circulation in the

mucous membrane probably have more to do with the production of flatulence than any other factor.

Schoen has pointed out that a big factor in lowering the amount of absorption is a drop in the tone of the muscle. For that reason the giving of pilocarpin which increases this tone may double the rate at which gases are absorbed. It may be that the meteorism of peritonitis is due largely to the loss of tone of the intestinal muscle and that some of the flatulence of asthenic women is due to weakness of the abdominal wall and low intra-abdominal pressure.

Interference with Intestinal Circulation. As was shown earlier in this chapter, when the mesenteric circulation is impaired, particularly on the venous side, the absorption of gases from the bowel is not only lessened but excretion from the blood is much increased. McIver and his associates, in their experiments, found that most of the gas in these loops is carbon dioxid. This seems to be due to the fact that what oxygen has been excreted into them has been called on to meet the increased demand for that gas on the part of the tissues.

Kader, Boycott, A. A. Strauss (1916) and others who have performed these experiments with closed loops and obstructed vessels have commented on the fact that it makes little difference whether the bowel is filled with feces, empty, or carefully washed; the amounts of gas that form are about the same. The great lesson that the surgeon should carry away is that when he is operating on the bowel he should desire not so much that it be clean as that it have a normal circulation and a normal gas exchange. As I showed years ago, these things can, in some persons, be seriously upset by purgatives (Alvarez, 1918[d], Alvarez and Taylor, 1917, and Taylor, Terry and Alvarez).

The accumulation of gas in the bowel that occurs when the circulation is interfered with, offers an attractive explanation for the appearance of flatulence in a number of diseases. To be sure, as McIver and his associates point out, the conditions in the experiments were more severe than they are in any disease except perhaps mesenteric thrombosis, but still I think the findings are suggestive, especially since Schoen

has told us why the colon is so much more likely to bloat with circulatory disturbances than is the small bowel.

Flatulence is one of the early symptoms of heart failure, and some persons bloat almost immediately when they become dyspneic or when an abnormal type of heart rhythm makes its appearance. The suddenness with which the flatulence appears, and the fact that it comes before much if any venous stagnation can be demonstrated, makes it seem probable that the mechanism is often a nervous one and similar to that which produces the marked degrees of flatulence seen in certain persons under excitement, or in the presence of fear and worry. The man, however, whose liver is showing the effects of back pressure or whose lips are definitely cyanotic should develop flatulence on account of the impaired gas exchange in the colon. It may be also that differences in the tension of the blood gases such as have been shown by Stewart to develop shortly after the onset of auricular fibrillation can upset the gas balance in the wall of the bowel before venous stagnation has developed. The flatulence of nervous persons might be due at least in part to upsets in the gas exchange of the bowel, associated with an internal blushing and blanching similar to that which takes place so commonly in the skin.

One can think of changes not only on the arterial side of the intestinal circulation but also on the venous. Unfortunately, we know little about the pressure in the portal vein (F. P. Mall, 1890, 1892), but some observers have seen big rises after stimulation of the roots of from the fifth to the ninth dorsal nerves. The path is apparently through the splanchnics (Bayliss and Starling, 1894; Mall). Stookey has described cases of tumor of this part of the cord in which there was severe abdominal distention, but we cannot be sure what the mechanism was.

Theoretically, flatulence ought to be a prominent symptom in cases of cirrhosis of the liver, but apparently it does not always develop. Dr. McVicar tells me that the French clinicians have a saying that in cirrhosis, "the wind comes before the rain," but it is hard to say how much the frequently associated cholecystitis has to do with this flatulence.

Certainly, a good many persons with badly damaged livers make no complaint about gas.

A drop in the intra-intestinal or intra-abdominal pressure such as takes place in paralytic ileus or in conditions associated with relaxation of the muscles of the abdominal wall can lead to the poor absorption of intestinal gases; and conversely, an increase in abdominal pressure such as can be secured perhaps with the help of a good corset, might help in getting rid of them (Schoen).

According to Talma, the sudden tympanites of the hysterical is due to a simultaneous contraction of the diaphragm and a relaxation of the abdominal wall. Whether this is true or not could be learned by making a roentgenographic examination of the abdomen in the case of a few of these women. To my mind it is an interesting fact, and worthy of further study, that no increase in the amount of abdominal gas can be made out with the roentgen ray in many persons who feel sure that they are distended.

Similarly, the patient with duodenal ulcer often thinks that his hunger distress is due to gas, but the roentgenoscopic examination suggests that his nerves are playing a trick on him. Very commonly in my experience, the gas which is thought to be in the stomach is really in the splenic flexure of the colon, and after the roentgen-ray examination, it is obvious why the patient cannot get rid of it by belching. In textbooks it is stated that the tympanic note of Traube's semilunar space is produced by gas in the stomach, but in my experience it is generally due to gas in the splenic flexure.

Interference with the Gas-carrying Power of the Blood. Dr. Giffen tells me that flatulence is not a common symptom in pernicious anemia and, when present, it may be due to gallbladder disease or some other abdominal lesion. It seems therefore that the hemic factor in flatulence must be an insignificant one.

Interference with Exhalation from the Lungs. It is well known that flatulence with abdominal distention can become a serious complication during the course of pneumonia, but it may of course be due simply to the paralyzing effect of the toxins on the bowel. It is suggestive that Boothby

so far has had little or no trouble with flatulence in a series of patients with severe pneumonia treated in a chamber containing 50 per cent oxygen. In such an atmosphere, more of the nitrogen in the bowel would diffuse out and less would be left to cause trouble in the bowel. A study of the blood gases in pneumonia has been made by Hastings, Neill, Morgan, and Binger.

ACUTE DILATATION OF THE STOMACH

Acute dilatation of the stomach is a condition which not infrequently causes death after operations, if the surgeon is not on the lookout for it. On several occasions, while working with animals with the abdomen open I have seen it develop rapidly. This was generally when the animal had been under anesthesia for several hours and the tone of the stomach was beginning to drop. In some cases it was due definitely to a peculiar type of powerful respiratory movement which rapidly filled the stomach with air. Deflation could not take place on account of a valvelike obstruction somewhere near the cardia. As I could feel that the cardia was relaxed it seemed clear that the obstruction must be at the diaphragm, and when I succeeded in flattening the stomach back against the spine, the kink was straightened, and air and fluid shot out through the animal's mouth. Hedblom and Cannon once produced the condition in a cat by injecting croton oil into the cecum, and Woodyatt and Graham produced it by tying some of the vessels to the stomach, closing the animals for fourteen hours and then opening them again. The second anesthetic was sometimes enough to produce the dilatation. In the case of three acutely dilated human stomachs, the fluid removed seemed to be a bloody exudate, and the gas was made up of CO_2, 24 per cent, O_2, 4 per cent, and N, 72 per cent. This analysis showed that the gas could not all have been swallowed air, and it was not due to fermentation of the contents, as in that case it would have contained some CH_4.

The essential thing to remember clinically is that these patients can generally be saved if their stomachs are promptly washed out. Apparently in some cases there is an obstruction

of the third portion of the duodenum by the root of the mesentery, an obstruction that is relieved when the patient lies prone.

BORBORYGMI

Often, while watching the intestines of animals opened under salt solution, I have noticed the production of noises by strong peristaltic contractions which, after putting considerable pressure on the intestinal contents, suddenly let go and allowed the material to squirt backward through the relaxing ring. Cannon has observed the same sort of thing while watching the stomachs of cats with the roentgen ray. He spent some time studying these gastrointestinal sounds with the hope that a knowledge of them might be helpful to practitioners of medicine (Cannon, 1905). The sounds of the stomach are most audible when the subject is reclining in such a way as to bring the gas bubble into the pars pylorica. In man they may continue with monotonous regularity for two hours or more after a large meal. Occasionally there are silent intervals when a wave seems to drop out.

The rhythmic sounds of the small intestine are different in quality from the gushing, explosive sounds of the stomach: they are either soft crepitations, rattling explosive discharges, or sometimes slow rumbles. In man, these sounds recur from 7 to 12 times a minute. They can be heard best in the lower left quadrant of the abdomen, and especially at times when the stomach is quiet. Cannon could hear also some gurgling sounds due probably to contractions of the colon. These recurred at fairly long, rather irregular intervals. After giving the subject an enema, they came with cramplike pains which recurred at intervals of from fifteen to fifty-four seconds. The right side of the colon seemed to be by far the most active part. There are other sounds to be heard in the abdomen which are not rhythmic: little popping noises as if bubbles of gas were bursting.

THE ACTION OF CARMINATIVES

Some light might be thrown on the mechanism of flatulence if we could learn more about the way in which carminatives

act. Theoretically they might stimulate peristalsis so that the gas would be passed onward, or they might increase the rate of absorption either by improving the circulation in the mucous membrane or by increasing the tension of the muscle. The experiments of Plant and Miller with some of the carminative oils suggest that they produce relaxation of the wall of the stomach and at the same time an increase in the tone and activity of the whole bowel. Muirhead and Gerald studied the effect of the commoner volatile oils on isolated segments of intestine and found that a number of them produced quite marked stimulation, in dilutions of about 1 to 35,000, and all produced relaxation in dilutions of about 1 to 7500.

Unfortunately such work can only be suggestive, and what is needed is a careful and extended study with the roentgen ray to see what happens to the digestive tract and to the gas when carminatives, given by mouth, bring relief. Pokorny studied the effect of charcoal on intestinal gases and came to the conclusion that it does not act by absorption of the gas but by the absorption of some harmful thing which produces gas. She gave it to patients with the hope of getting rid of gas and thus securing better roentgenograms of the liver and kidneys.

CHAPTER XXVII

TECHNICAL METHODS AND APPARATUS

As much of the technic for the experiments described in this book had to be worked out as I went along, and as many details which I learned from Dr. Cannon and others are not to be found in textbooks, it occurred to me that a short chapter on apparatus and methods might be gratefully received, particularly by beginners in this field of research.

Fig. 94. H. Sanders, Ezn.

As Cannon and Auer have pointed out, the early physiologists were greatly hampered in their study of the intestinal movements by the fact that the opening of the abdomen has a strong inhibiting effect. For this reason most of their conclusions were based on observation of the powerful writhing movements that appear just after the death of an animal. The early studies have little value also because the bowel was allowed to dry in the air; and we know that that has a disturbing effect. In 1871, Sanders and Van Braam Houckgeest made a big improvement by opening

the animals under a bath of salt solution. That prevented the drying, but conditions were still not entirely normal. Much work was done with fistulae into various parts of the tract and with balloons passed through the mouth, but here again many objections can be raised.

THE ROENTGEN RAY AND THE BARIUM MEAL. It was not until 1896, when Prof. Bowditch suggested to Cannon, then a student, that he use the newly discovered roentgen ray, that we were supplied with an entirely trustworthy method for studying the movements of the alimentary

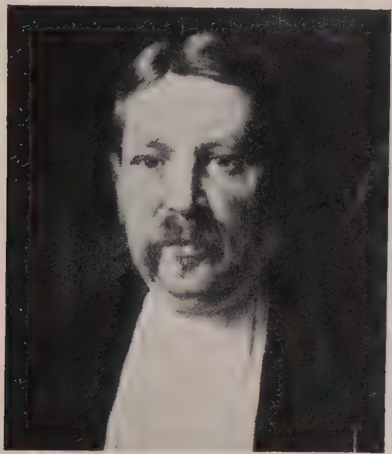

FIG. 95. J. P. Van Braam Houckgeest.

canal (Bowditch, and Cannon, 1898). Incidentally, it should be noted that it is this method which is now being used so universally and so satisfactorily in medical practice on man. As this technic for animals is well described by Cannon (1911[a]), I shall not go into details here. Barium sulfate "for *x*-ray use" is now used instead of the bismuth subnitrate which occasionally becomes toxic in the bowel. The best animals to use are tame old female cats which will not object to handling, because any anger or excitement stops the intestinal movements. The most satisfactory apparatus consists of a small transformer and a self-rectifying Coolidge tube. Great care should be taken to see that the operator is

protected from all stray radiations and from contact with the high tension wires. The room must be absolutely dark and after entering it the student should not attempt to work for half an hour or more until his retina is fully adjusted. The roentgen-ray method is now little used by physiologists, probably because there is little hope of seeing anything new which Cannon or the many clinical roentgenologists have not already described. I think, however, that it should be used more and more by the pharmacologists.

Method of Auer. Auer made a number of interesting observations on rabbits whose abdomens were shaved. He found he could watch the movements of the cecum quite satisfactorily through the thin abdominal wall. Similarly, I have been able to study rhythmic segmentation in persons with large hernias, where the bowel lay under a thin coat of peritoneum and skin. (See also Rossbach, 1890[b].)

Gastric and Duodenal Tubes. For this technic the reader is referred particularly to the articles by Carlson (1916) and his associates. They have done much excellent physiologic work on the movements of the human stomach, using these tubes and balloons; in most of it they have been concerned with the hunger contractions and with secretion. Wheelon and Thomas (1920) pointed out that a balloon which can slip around in the stomach is not likely to give an entirely satisfactory record of what is going on there, so they anchored a special type of metal tambour in the antrum and in the pyloric canal. McClendon (1915[a], p. 180) has studied the hydrogen-ion concentration of the gastric and intestinal juices by letting down a specially designed electrode on the end of a wire.

Fistulae. First should be mentioned the Heidenhain-Pavloff stomach which is so designed that the experimenter can study gastric secretion under many conditions. A flap of stomach wall is dissected up and formed into a pouch which empties externally through a fistula. This technic will be found described in the first chapter of Pavloff's book on "The Work of the Digestive Glands," and in excellent articles in the *Ergebnisse der Physiolgie* (1902), in Tigerstedt's "Handbuch der Physiologischen Methodik," in Bickel and

Katsch's "Chirurgische Technik zur normalen und pathologischen Physiologie des Verdauungsapparates," and in articles by Ivy (1926) and Mann. It has recently been used to great advantage by Ivy (1926). In order to obtain pure gastric juice, Pavloff performed the operation of esophagotomy on dogs already possessing a gastric fistula; that is, he divided the esophagus in the neck and allowed the upper end to heal into the skin incision. When such dogs are given food it drops out of the esophageal opening, but the psychic stimulus causes a flow of gastric juice.

Thiry studied the intestinal juices by closing off one end of a loop of bowel and sewing the other to an opening in the abdominal wall. Vella brought both ends into the skin incision so as to be able to study the progress of balls and bits of food through the loop. Others have made fistulae into various parts of the intestine in order to study the pyloric function and the succus entericus (Cohnheim and Dreyfus, 1908[a], Best and Cohnheim, 1910[a], 1911, Baumstark, London, Thomsen, Baumstark and Cohnheim, von Mering, 1893, Hirsch, 1893[b]). Especially when making duodenal fistulae it is helpful to have the stoma as near as possible to the spine of the animal so that gravity will favor and not hinder the keeping of the animal clean. Another method is to sew the unopened bowel to the skin and then to introduce or remove material with a large hypodermic syringe, the needle of which is thrust through the wall (Carnot, 1907).

Windows. Van Braam Houckgeest tried to use glass windows in the abdominal wall, and others (Sabbatani, Katsch, 1913, Katsch and Borchers, 1913[a], and Zondek) have since done considerable work with animals that have been operated on in this way. Watch glasses or pieces of celluloid are generally used, and with care the animals can be kept alive and well for some time. They are useful for pharmacologic studies or for class demonstrations.

Opening under Salt Solution. For the careful analysis of the intestinal movements it seems to me that we shall have to turn more and more to the method which was devised and first used by Sanders. As his papers were published in a small Dutch journal they dropped into oblivion,

and the technic is generally ascribed to Van Braam Houckgeest. Sanders' article shows considerable ability; and it is interesting that he was the first to describe reverse peristalsis in the colon. Houckgeest's article is also well worth reading today. Only with the animal opened can one get the kymographic records which are so essential for the exact analysis of muscular movements and conduction; and only in this way can one orient himself properly so as to know what part of the bowel is being studied; which end is orad, etc.

Rabbits and cats can be anesthetized most conveniently with urethan, 2 grams per kg. by mouth or rectum. A catheter can be passed into the esophagus through a hole in a small spindleshaped gag. Every care should be taken to see that this catheter gets into the stomach and not into the trachea. If the animal should show any signs of returning sensation, more urethan should be injected through a fine needle into the duodenum. After the animal is thoroughly anesthetized a canula may be put into the trachea, although this is not always necessary.

In order to avoid much of the inhibition that comes from opening the abdomen (see Hotz, and Meltzer) the spinal cord should generally be destroyed from a point just above the sacrum to the interscapular region. A small incision is made over the lower lumbar spine; an opening is made between two laminae and a large copper wire is thrust up through the canal as far as the interscapular region. The wound is then closed with a suture. The greatest care should be taken while opening the abdomen to cut exactly in the median line. Only in this way can one avoid hemorrhage which is hard to stop in the bath, and which can soon obscure the field of vision. The animal should be washed and then put into the bath. I use a copper tank, 8 inches wide, 9½ inches deep, and 31 inches long, with an electric heater and thermo-regulator.

Each of the animal's paws is held by a thong which runs to the eyelet on the lower end of a rod which can be held in any desired position by the simple clamp pictured in Figure 98. Jacobj (1890) used a vertical tank which he thought had certain advantages. It had a glass window on one side

through which the bowel could be observed. The bath should consist either of 0.8 per cent sodium chlorid solution or else Locke's solution of the following composition:

$NaCl$	9.00
KCl	.42
$CaCl_2$ anhydrous	.24
$NaHCO_3$	.20
H_2O	1000.00

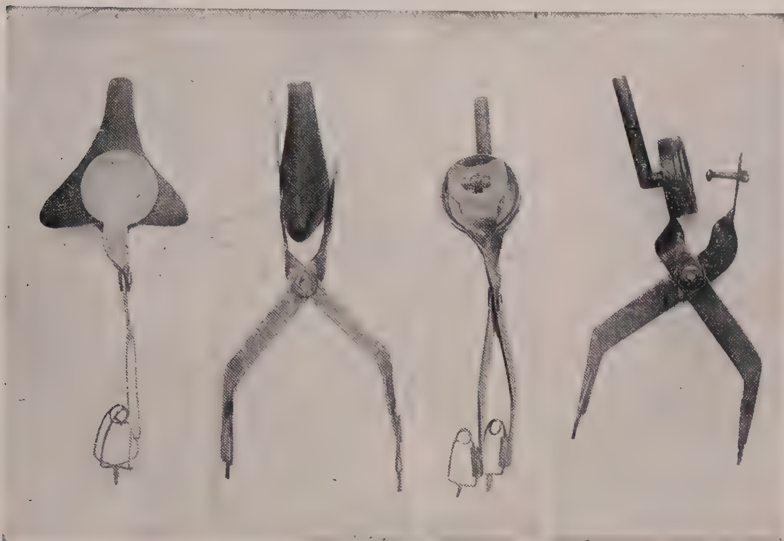

FIG. 96. On the left is shown the simple type of recorder ordinarily used. On the right is a similar one, made of silver with a small tambour instead of the rubber teat.

I now use the Locke's solution, although I do not know whether the results are any more satisfactory than those with plain salt solution. If good movements are to be obtained, the animal should be fed shortly before anesthetization. Some men give aloin or castor oil the night before, but Taylor and I (Alvarez and Taylor) have shown that purgation alters the gradients and damages the muscle in places. Every care should be taken to get normal and frisky animals. As defecation into the tank is often annoying when working

with cats, the rectum can be tied off with a piece of tape. The animal's head can be held in proper position by an ordinary Tschermak head-holder which is fastened to the edge of the tank.

Mechanical Recorders. The movements can be observed visually or they can be recorded mechanically by means of balloons or some form of enterograph. The use of balloons is unsatisfactory for several reasons. They are foreign bodies; they block the lumen of the gut; they cause bleeding; and the trauma incident to their introduction often overshadows any other stimuli that one may be trying to record. Of all the methods for recording intestinal contractions mentioned in Tigerstedt's "Handbuch der physiologischen Methodik," the one that comes nearest to the requirements for good work is the enterograph of Bayliss and Starling. This, however, is rather too elaborate; it is not easily fastened to the bowel wall, and it must be kept above the level of the salt solution.

Figure 96 shows on the left, a type of *enterograph* which I designed in 1913 and which has enabled me to get records from several parts of the bowel at one time. This simple and cheap little apparatus consists of two pieces of sheet aluminum, two short lengths of piano wire and a small rubber teat. I first used the teat which is made for springing the shutters in large commercial cameras. When the supply of these (from England) was cut off by the War, I used the triangular little bags that are supplied for the ends of stirring rods. The rubber teat should be cemented to the aluminum only on one side. When fastened on both sides it is likely to bind and the apparatus is less sensitive. The other arm of the lever is fastened to the peritoneal coat of the bowel by means of a little wire serrefine. This generally has to be made by the student himself if it is to grip firmly and not spring open all the time. A series of these recorders can be fastened to a number of tambours which write one above the other on a smoked surface.

For a while, during the War, when I could not get any form of rubber teat I fastened a small tambour to one side of the enterograph as shown in the figure, but I found this

less sensitive than the much cheaper and simpler form. The little serrefines are much more convenient than any form of hook or sewed-on apparatus because the tone of the bowel changes rapidly from time to time and the observer must be able to take up slack quickly and without undue handling. The only place where the recorders do not work well is on the colon. That contracts down so hard at times that it tears

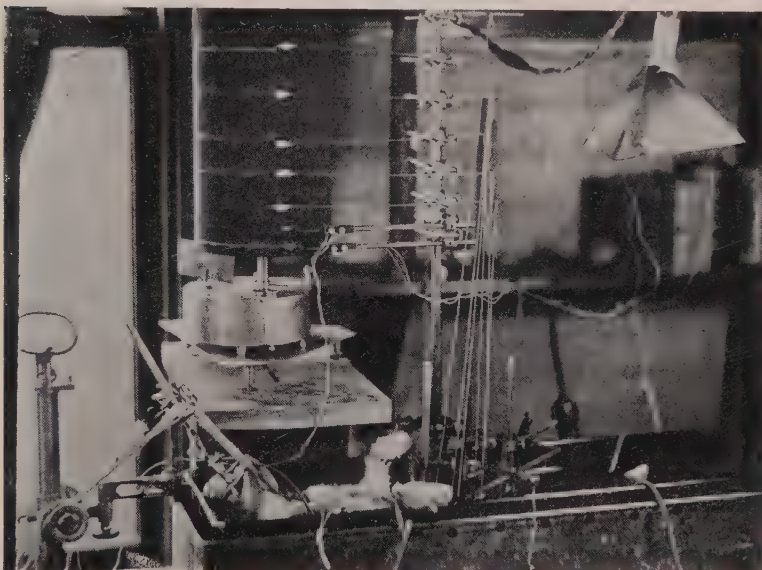

Fig. 97. Shows an animal in the tank with the abdomen open and records being obtained simultaneously from several points on the stomach and bowel.

away from the instruments, leaving them hanging to shreads of peritoneum.

Much better records can be secured with the method described by Alvarez and Mahoney (1924). From six to ten places on the stomach or bowel are seized by little wire serrefines which are fastened to the ends of the horizontal arms of "L" rods which serve to hold the several segments in place under the bath. Other similar serrefines are attached nearby in such a way that either the circular or the longi-

tudinal fibers (as desired) will pull on threads which run up to light levers recording one above the other on a smoked drum (Fig. 97).

Slowtzoff, Trendelenburg (1913) and others have described methods for recording the contractions of a loop of bowel through holes made in the abdominal wall of an anesthetized animal, but I can see no advantages over the tank method if a tank is available. Courtade and Guyon used loops of bowel removed from the abdomen but still attached by a section of mesentery. Hofmeister and Schütz did work with the excised stomach in a moist chamber. I have found it con-

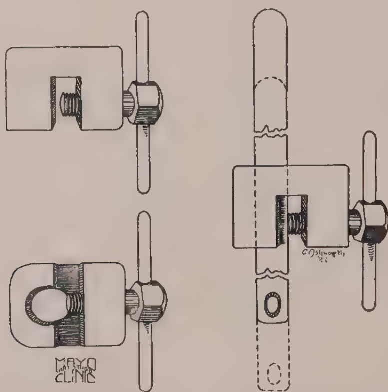

Fig 98. Clamp designed to hold a rod to the side of the tank in which animals are opened under warm salt solution.

venient to run steam from a flask of boiling water into such a chamber; it not only keeps the tissue moist, but it keeps it warm. Sick and Tedesko studied the excised stomach in oxygenated Locke's solution and Carnot (1913) and Carnot and Glenard perfused the intestine excised from the body as a whole.

Small Excised Segments. Haffter seems to have been the first to learn that excised segments of intestine will continue to contract rhythmically, but Magnus (1904[a]) deserves most credit for having worked out the details of the method which now goes by his name. I have modified

it to the extent that I use several segments at a time in the same bath. The animal is killed with chloroform or with a blow on the head. It is then opened, and pieces from 25 to 50 cm. in length are removed from various parts of the bowel and strung on a safety pin in proper order, and with the orad end toward the pin. These segments can then be kept in iced Locke's solution and smaller pieces cut off as needed during the day.

I generally use at least five segments at one time, suspended between serrefines in a beaker containing about 400 c.c. of Locke's solution. This is kept in a water bath at 38° c. It is oxygenated by a small stream of compressed air which bubbles through it. When four or five segments are used at one time they should be cut fairly short; that is, about 2 cm. long, and special levers should be used. The Harvard Apparatus Company made me some, 30 cm. long, with an adjustable pivot so that the ratio between the arms can be varied at will. If the ordinary heart levers are used, the magnification is so great that all the records will not go on a drum of standard size.

If a large amount of Locke's solution is used, the segments contract more regularly and for a longer period of time, probably because their metabolites are well diluted. It is only when using rare drugs or small amounts of vital fluids that one needs to use a smaller amount of solution. As I have pointed out before (Alvarez, 1914), when making pharmacologic studies with such small amounts, one must be careful to see that the temperature remains constant within tenths of a degree; otherwise erroneous conclusions may easily be drawn. Whenever possible, the pharmacologist should use several segments at one time to serve as checks, one on another. Anyone who will look over some of the figures in my sixteenth article (Alvarez, 1918[c]) will, I think, be impressed with the need for that precaution.

When studying conduction, the myenteric reflex and other phenomena, the technique described in my eighteenth article (Alvarez and Starkweather, 1919) is very useful. There I show how records can be obtained from both ends of a segment by turning them up like a U.

Sometimes it is desired to compare the contractions of the circular and longitudinal muscles, or to study the action of drugs on the inner surface of the bowel. For such work the student may use the technic described by Gayda and Morishima and Fujitani.

For the *latent period work* I have used a simple moist chamber made out of a wide-mouthed six-ounce bottle. The

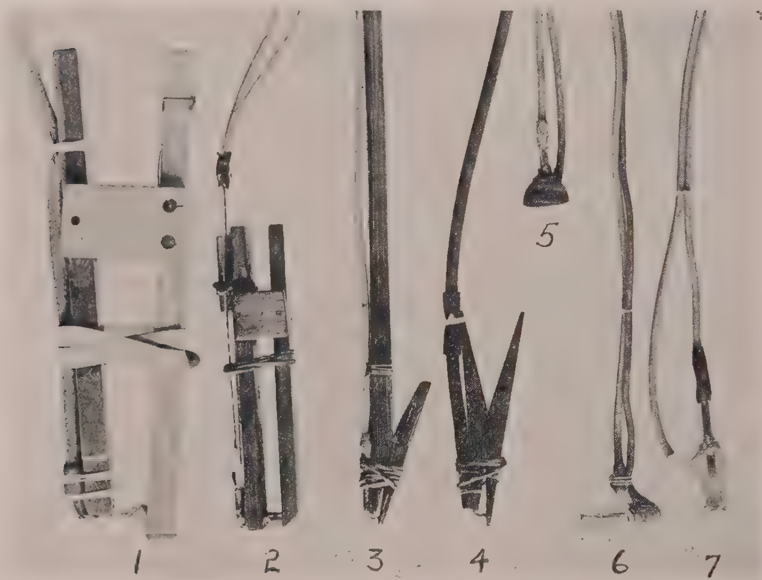

FIG. 99. Shows 1. A large wooden clamp and electrode used mainly for work on the lesser curvature of the stomach. 2. Small double electrode. 3. Electrode and clamp for holding immovable a place on the stomach or bowel. 4. Small clamp and electrode most commonly used. 5, 6, 7. Various types of suction electrode; one tube carries the wire and the other maintains suction.

lower end of the segment is fastened by a serrefine to a metal "L" support which is thrust through the rubber stopper. The other end of the segment is fastened to the metal heart lever by means of a fine copper wire. The current can be led to the segment through these two metal connections. The apparatus for the metabolic work and the catalase experiments will be found described in articles by Miss Starkweather and me (1918[a]).

ELECTROGRAMS. The apparatus and technic for electro-gastrographic work have been described in articles by Alvarez and Mahoney (1922[a]), Alvarez (1924[a]), and Richter. Figure 99 shows the various types of non-polarizable electrodes used.

MOTION PICTURES. As was pointed out in Chapter XIII, I am now finding it most helpful to record the movements of the stomach and bowel with the help of motion pictures. The camera, either a Bell and Howell Filmo or an Eastman Ciné-Kodak, is fastened in a specially made clamp which slides on the edges of the tank and keeps the lens 30 or more centimeters above the tissues being photographed. Various points on the surface of the stomach and bowel are marked by inserting under the peritoneal coat a short piece of fine black thread. Illumination is supplied by two Bell and Howell Filmolites.

For measuring the individual pictures we use a small Kodascope with an extra switch inserted to stop the motor. This Kodascope is placed on a stand about 3 feet above a desk and with the help of a reflecting prism the images are thrown down onto a piece of white paper where the distances between points on stomach and bowel can easily be taken off with dividers and plotted on coordinate paper.

REFERENCE ARTICLES. The student who plans to do research work in gastroenterology or the physician who wishes to know more about the mechanical factors of digestion should study carefully Cannon's classic book on the subject. Bayliss and Starling's three articles, and one by Elliott and Barclay-Smith should also be read and re-read. Magnus' articles in the *Ergebnisse*, and in Tigerstedt's "Handbuch," are also very helpful. Much good physiology will be found in excellent books and articles by Carman, Barclay, Carlson, Case, and Hurst.

For information on the chemical side of digestion the student should turn to the splendid books of Pavloff, Cohnheim, London, Taylor, and Babkin. Babkin was Pavloff's assistant at Petrograd, and his book summarizes the work done in Russia up to the beginning of the War.

Todd's splendid little book presents the anatomy of the digestive tract from the viewpoint of a man who is thoroughly conversant with the work of the physiologist and the roentgenologist. Those who would like to know something about the comparative anatomy of the tract should turn to Oppel, Huntington, and Mitchell. The subject of comparative physiology has been well covered by Jordan.

FIG. 100. Ivan P. Pavloff.

The real student of a subject must always know something about its history and development. Access to the older literature can easily be obtained through the little book of Poensgen; and the articles of Cary, Pearce, Cannon (1914) and Crane will be found very interesting. American students will be interested also in the work of Beaumont, the "backwoods physiologist." His book contains little of scientific interest for us today, but it makes up for it in the wealth of inspiration which it can give to any young man who, with little outside help or recognition, is struggling onward with his work.

BIBLIOGRAPHY

ABEL, W. Further observations on the development of the sympathetic nervous system in the chick. *J. Anat. & Physiol.*, 1912, xlvii, 35–72.

ALVAREZ, W. C. Functional variations in contractions of different parts of the small intestine. *Am. J. Physiol.*, 1914, xxxv, 177–193.

ALVAREZ, W. C. (a) Further studies on intestinal rhythm. *Am. J. Physiol.*, 1915, xxxvii, 267–281.

ALVAREZ, W. C. (b) The motor functions of the intestine from a new point of view. *J. Am. M. Assn.*, 1915, lxv, 388–394.

ALVAREZ, W. C. (a) Differences in rhythmicity and tone in different parts of the wall of the stomach. *Am. J. Physiol.*, 1916, xl, 585–602.

ALVAREZ, W. C. (b) Differences in irritability and latent period in different parts of the wall of the stomach. *Am. J. Physiol.*, 1916, xli, 321–332.

ALVAREZ, W. C. (a) Differences in latent period and form of the contraction curve in muscle strips from different parts of the frog's stomach. *Am. J. Physiol.*, 1917, xlii, 422–434.

ALVAREZ, W. C. (b) Differences in latent period and form of the contraction curve in muscle strips from different parts of the mammalian stomach. *Am. J. Physiol.*, 1917, xlii, 435–449.

ALVAREZ, W. C. (c) The syndrome of mild reverse peristalsis. *J. Am. M. Assn.*, 1917, lxix, 2018–2024.

ALVAREZ, W. C. (a) Differences in the action of drugs on different parts of the bowel. *J. Pharmacol. & Exper. Therap.*, 1918, xii, 171–191.

ALVAREZ, W. C. (b) Differences in the behavior of segments from different parts of the intestine. *Am. J. Physiol.*, 1918, xlv, 342–350.

ALVAREZ, W. C. (c) The influence of drugs on intestinal rhythmicity. *Am. J. Physiol.*, 1918, xlvi, 554–562.

ALVAREZ, W. C. (d) Is the purgation of patients before operation justifiable? *Surg., Gynec. & Obst.*, 1918, xxvi, 651–659.

ALVAREZ, W. C. (a) The origin of the so-called autointoxication symptoms. *J. Am. M. Assn.*, 1919, lxxii, 8–13.

ALVAREZ, W. C. (b) The metabolic gradient underlying peristalsis. *J. Am. M. Assn.*, 1919, lxxiii, 1438–1440.

ALVAREZ, W. C. (c) Recent advances in gastric physiology. *Am. J. M. Sc.*, 1919, clviii, 609–619.

ALVAREZ, W. C. Peristalsis in health and disease. *Am. J. Roentgenol.*, 1921, viii, 1–11.

ALVAREZ, W. C. (a) The electrogastrogram and what it shows. *J. Am. M. Assn.*, 1922, lxxviii, 1116–1119.

ALVAREZ, W. C. (b) New methods of studying gastric peristalsis. *J. Am. M. Assn.*, 1922 lxxix, 1281–1284.

ALVAREZ, W. C. New light on gastric peristalsis. *Am. J. Roentgenol.*, 1923, x, 31–35.

ALVAREZ, W. C. (a) Bayliss and Starling's law of the intestine or the myenteric reflex. *Am. J. Physiol.*, 1924, lxix, 229–248.

ALVAREZ, W. C. (b) A non-polarizable electrode and clamp designed particularly for gastro-intestinal work. *Am. J. Physiol.*, 1924, lxix, 249–253.

ALVAREZ, W. C. (c) Intestinal autointoxication. *Physiol. Rev.*, 1924, iv, 352–393.

ALVAREZ, W. C. Tonus rhythms in the bowel. *Am. J. Physiol.*, 1925, lxxiv, 181–187.

ALVAREZ, W. C. A practical treatment of duodenal ulcer. *J. Am. M. Assn.*, 1926, lxxxvii, 2086–2089.

ALVAREZ, W. C. Reverse waves in the pars pylorica of the stomach. *J. Am. M. Assn.*, 1927, lxxxviii, 472–473.

ALVAREZ, W. C. and FREEDLANDER, B. L. The rate of progress of food residues through the bowel. *J. Am. M. Assn.*, 1924, lxxxiii, 576–580.

ALVAREZ, W. C. and MAHONEY, L. J. (a) Action currents in stomach and intestine. *Am. J. Physiol.*, 1922, lviii, 476–493.

ALVAREZ, W. C. and MAHONEY, L. J. (b) The myogenic nature of the rhythmic contractions of the intestine. *Am. J. Physiol.*, 1922, lix, 421–430.

ALVAREZ, W. C. and MAHONEY, L. J. The relations between gastric and duodenal peristalsis. *Am. J. Physiol.*, 1923, lxiv, 371–386.

ALVAREZ, W. C. and MAHONEY, L. J. Peristaltic rush in the rabbit. *Am. J. Physiol.*, 1924, lxix, 211–225.

ALVAREZ, W. C. and STARKWEATHER, E. (a) The metabolic gradient underlying intestinal peristalsis. *Am. J. Physiol.*, 1918, xlvi, 186–208.

ALVAREZ, W. C. and STARKWEATHER, E. (b) The motor functions of the cecum. *Am. J. Physiol.*, 1918, xlvi, 563–569.

ALVAREZ, W. C. and STARKWEATHER, E. (c) Differences in the catalase content of muscle from different parts of the stomach. *Am. J. Physiol.*, 1918, xlvii, 60–66.

ALVAREZ, W. C. and STARKWEATHER, E. (d) The catalase content of the mucous membrane from different parts of the digestive tract. *Am. J. Physiol.*, 1918, xlvii, 67–75.

ALVAREZ, W. C. and STARKWEATHER, E. (e) The metabolic gradient underlying colonic peristalsis. *Am. J. Physiol.*, 1918, xlvii, 293–301.

ALVAREZ, W. C. and STARKWEATHER, E. Conduction in the small intestine. *Am. J. Physiol.*, 1919, l, 252–265.

ALVAREZ, W. C. and TAYLOR, F. B. Changes in rhythmicity, irritability and tone in the purged intestine. *J. Pharmcol. & Exper. Therap.*, 1917, x, 365–377.

ALVAREZ, W. C. and ZIMMERMANN, A. Gastric wavelets. *Am. J. Physiol.*, 1926, lxxviii, 405–410.

APPERLY, F. L. The use of hydrochloric acid and sodium bicarbonate in the treatment of certain common diseases. *M. J. Australia*, 1926, i, 354–358.

ARLOING, S. and CHANTRE, E. Recherches physiologiques sur le muscle sphincter ani; particularité offerte par son innervation et sa contraction réflexes. *Compt. rend. Soc. de biol.*, 1897, cxxiv, 1206–1210.

ARMBRUSTER, Th. Beiträge zur Pathogenese des chronischen Magengeschwürs. *Beitr. z. klin. Chir.*, 1922, cxxvi, 390–399.

Arnold, L. An experimental method for the study of the bacterial flora and the hydrogen-ion concentration of the gastro-intestinal tract. *Arch. Path. & Lab. Med.*, 1926, i, 839.

Aschoff, L. Lectures on Pathology. New York, 1924.

Auer, J. Gastric peristalsis in rabbits under normal and some experimental conditions. *Am. J. Physiol.*, 1907, xviii, 347–361.

Auerbach, L. Ueber einen Plexus myentericus, einen bisher unbekannten ganglio-nervösen Apparat im Darmkanal der Wirbelthiere. Breslau, 1862.

Auerbach, L. Fernere vorläufige Mitteilung über den Nervenapparat des Darmes. *Arch. f. path. Anat.*, 1864, xxx, 457–460.

Aufschnaiter, O. V. Die Muskelhaut des menschlichen Magens. *Wien. Sitzungsb. d.k. Akad. d. Wissensch.*, 1894, ciii, Abth. 3, 75–96.

Auster, L. S. and Crohn, B. B. Notes on studies in the physiology of the gall-bladder. *Am. J. M. Sc.*, 1922, clxiv, 345–360.

Austin, A. E. Diseases of the Digestive Tract and their Treatment. St. Louis, 1916.

Babkin, B. P. Die äussere Sekretion der Verdauungsdrüsen. Berlin, 1914.

Babkin, B. P. The influence of natural chemical stimuli on the movements of the small intestine. *Physiolog. Abstracts*, 1917, ii, 42–43.

Babkin, B. P. The influence of natural chemical stimuli on the movements of the alimentary canal. *Can. M. Assn. J.*, 1925, xv, 719–724.

Babkin, B. P. The physiological factors determining the acidity of the gastric juice and of the gastric contents. *Canad. M. J.*, 1927, xvii, 36–42.

Bainbridge, F. A. and Dale, H. H. The contractile mechanism of the gall-bladder and its extrinsic nervous control. *J. Physiol.*, 1905, xxxiii, 138–155.

Baird, M. Mc., Campbell, J. M. H. and Hern, J. R. B. The importance of estimating chlorides in the fractional test meal samples, and some experiments with the duodenal tube. *Guy's Hosp. Rep.*, 1924, lxxiv, 23–54.

Baldwin, W. M. The pancreatic ducts in man, together with a study of the microscopical structure of the minor duodenal papilla. *Anat. Record*, 1911, v, 197–228.

Balfour, D. C. The case against gastroenterostomy. *J. Am. M. Assn.*, 1924, lxxxiii, 603–606.

Balfour, D. C. The occurrence and management of gastrojejunal ulcer. *Ann. Surg.*, 1926 lxxxiv, 271–280.,

Balint, R. and Benedict, H. Über Erkrankungen des Conus terminalis und der Cauda equina. *Deutsche Ztschr. f. Nervenh.*, 1906, xxx, 1–43.

Bancroft, F. W. and Esterly, C. O. A case of physiological polarization of the ascidian heart. *Univ. Calif. Pub. Zool.*, 1903, i, 105–114.

Barbera, A. G. Über die Riezbarkeit des Froshmagnes. *Ztschr. f. Biol.*, 1898, xxxvi, 239–258.

Barclay, A. E. The normal and pathological stomach as seen by the *x*-rays. *Brit. M. J.*, 1910, ii, 537–541.

Barclay, A. E. Note on the movements of the large intestine. *Arch. Roentg. Ray*, 1912, xvi, 422–424.

Barclay, A. E. (a) The etiology of gastric ulcer. *Arch. Roentg. Ray*, 1913, xviii, 234–238.

Barclay, A. E. (b) The Stomach and Esophagus. London, 1913.

Barclay, A. E. Gastric borborygmi. *Arch. Roentg. Ray*, 1914, xix, 172–173.

Barclay, A. E. Radiological studies of the large intestine. *Brit. J. Surg.*, 1915, ii, 638–652.

Barratt, W. On the anatomical structure of the vagus nerve. *J. Anat. & Physiol.*, 1898, xxxii, 422–427.

Barsony, T. and Egan, E. Über den duodenalen Pylorusreflex nach Röntgenuntersuchungen am Menschen mit der Gastroduodenal-Doppelsonde. *München. med. Wchnschr.*, 1925, lxxii, 1242–1244.

Bassler, A., Luckett, W. H. and Lutz, J. R. Some experiences with the Meltzer-Lyon method of draining the biliary system. *Am. J. M. Sc.*, 1921, clxii, 674–687.

Basslinger, J. Rhythmische Zusammenziehungen an der Cardia des Kaninchenmagens (Cardiapuls). *Untersuch. z. Naturlehre d. Menschen u. Tiere.* 1860, vii, 359–366.

Bauer, K. H. Magenstrasse und Magenulkus, Zugleich ein Beitrag zur Frage der Exstirpation der Magenstrasse. *Beitr. z. klin. Chir.*, 1925, cxxxv, 223–252.

Baumstark, R. Über Hervorrufung von Magenfunktions-störungen vom Darm aus. *Ztschr. f. physiol. Chem.*, 1913, lxxxiv, 437–450.

Baumstark, R. and Cohnheim, O. Zur Physiologie der Darmbewegungen und der Darmverdauung. *Ztschr. f. physiol. Chem.*, 1910, lxv, 483–488.

Bayliss, W. M. and Starling, E. H. On the origin from the spinal cord of the vaso-constrictor nerves of the portal vein. *J. Physiol.*, 1894, xvii, 120–128.

Bayliss, W. M. and Starling, E. H. The movements and innervation of the small intestine. *J. Physiol.*, 1899, xxiv, 99–143.

Bayliss, W. M. and Starling, E. H. The movements and innervation of the large intestine. *J. Physiol.*, 1900, xxvi, 107–118.

Bayliss, W. M. and Starling, E. H. The movements and innervation of the small intestine. *J. Physiol.*, 1901, xxvi, 125–138.

Beattie, J. The early stages of the development of the ileo-colic sphincter. *J. Anat.*, 1924, lix, 56–59.

Beaumont, W. Experiments and Observations on the Gastric Juice and the Physiology of Digestion. Plattsburgh, 1833.

Bechtereff, von and Weinberg. Die Functionen der Nervencentra. Jena, 1908, i, 259.

Beer, E. and Eggers, C. Are the intestines able to propel their contents in an antiperistaltic direction? *Ann. Surg.*, 1907, xlvi, 576–588.

Beitzke. Zur Histologie der chronischen Gastritis. *Verhandl. d. deutsch. path. Gesellsch.*, 1914, xvii, 433–435.

Bellamy, A. W. Differential susceptibility as a basis for modification and control of early development in the frog. *Biol. Bull.*, 1919, xxxvii, 312–361.

Belou, P. Anatomia de los Conductos Biliares y de la Arteria Cistica. Buenos Aires, 1915.

Bensley, R. R. The cardiac glands of mammals. *Am. J. Anat.*, 1902, ii, 105–156.

Bercovitz, Z. and Rogers, F. T. The inhibitory effects of vagus stimulation on gastric motility in the turtle. *Am. J. Physiol.*, 1921, lv, 310.

Berg, B. N. and Jobling, J. W. The effect of division and transplantation of the common duct upon gall-bladder function. *Proc. Soc. Exper. Biol. & Med.*, 1927, xxiv, 434–435.

Berg, H. H. Die direkten Röntgensymptome des Ulcus duodeni und ihre klinische Bedeutung. *Ergebn. d. med. Strahlenforschung*, 1926, ii, 249–350.

Bergmann, G. von. Zur diagnostischen Bedeutung der Pylorusfunktion. *Zentralbl. f. Roentgenstrahlen*, 1913, iv, 1–5.

Bernheim, A. Movements of the intestines. *J. Am. M. Assn.*, 1901, xxxvi, 429–431.

Best, F. Über den Einfluss der Zubereitung der Nahrungsmittel auf ihre Verdaulichkeit. *Deutsches Arch. f. klin. Med.*, 1911, civ, 94–118.

Best, F. and Cohnheim, O. (a) Über Bewegungsreflexe des Magendarmkanals. *Ztschr. f. physiol. Chem.*, 1910, lxix, 113–116.

Best, F. and Cohnheim, O. (b) Über die Verweildauer von Flüssigkeit im Magen. *Ztschr. f. physiol. Chem.*, 1910, lxix, 117–124.

Best, F. and Cohnheim, O. (c) Über den Rückfluss von Galle in den Magen bei Fettfütterung. *Ztschr. f. physiol. Chem.*, 1910, lxix, 125–126.

Best, F. and Cohnheim, O. Zur Röntgenuntersuchung des Verdauungskanals. *München. med. Wchnschr.*, 1911, lviii, 2732–2734.

Bethe, A. Das Centralnervensystem von Carcinus Maenas. *Arch. f. mikr. Anat.*, 1898, li, 382–452.

Bethe, A. Allgemeine Anatomie und Physiologie des Nervensystems. Leipzig, 1903.

Beuttenmüller, H. Beobachtungen an einer Zoekalfistel. *München. med. Wchnschr.*, 1920, lxvii, 743–745.

Bickel, A. Die Pathologie der Sekretion und Motilität im Verdauungskanal. *Internat. Beitr. z. Path. u. Therap. d. Ernährungsstör*, 1910, i, 116–127.

Bickel, A. and Katsch, G. Chirurgische Technik zur normalen und pathologischen Physiologie des Verdauungsapparates. Berlin, 1912.

Biedermann, W. Zur Physiologie der glatten Muskeln. *Arch. f. d. ges. Physiol.*, 1889, xlv, 369–388.

Biedermann, W. Studien zur vergleichenden Physiologie der peristaltischen Bewegungen. I. Die peristaltischen Bewegungen der Würmer und Tonus der glatter Muskeln. *Arch. f. d. ges. Physiol.*, 1904, cii, 475–541.

Biedermann, W. Studien zur vergleichenden Physiologie der peristaltischen Bewegungen. II. Die locomotorischen Wellen der Schneckensohle. *Arch. f. d. ges. Physiol.*, 1905, cvii, 1–56.

Biedermann, W. Studien zur vergleichenden Physiologie der peristaltischen Bewegungen. III. Die Innervation der Schneckensohle. *Arch. f. d. ges. Physiol.*, 1906, cxi, 251–297.

Bine, R. and Schmoll, E. The treatment of gastric and duodenal ulcer. *Calif. State J. M.*, 1914, xii, 361–366.

Black, G. V. An investigation of the physical characters of the human teeth in relation to their diseases, and to practical dental operations, together with the physical characters of filling materials. *Dental Cosmos*, 1895, xxxvii, 469–484.

Boardman, W. W. A study of the bacteriological findings in the Lyon-Meltzer test. *Am. J. M. Sc.*, 1924, clxvii, 847–853.

Boehm, G. Ueber den Einfluss des Nervus sympathicus und anderer autonomer Nerven auf die Bewegungen des Dickdarmes. *Arch. f. exper. Path. u. Pharmakol.*, 1913, lxxii, 1–55.

Bokai, A. (a) Experimentelle Beiträge zur Kenntniss der Darmbewegungen. *Arch. f. Physiol.*, 1887, xxiii, 209–232.

Bokai, A. (b) Experimentelle Beiträge zur Kenntniss der Darmbewegungen. *Arch. f. exper. Path. u. Pharmakol.*, 1887, xxiv, 153–166.

Boldireff, W. (a) Über den Übergang der natürlichen Mischung des Pankreas, des Darmsaftes und der Galle in den Magen. Die Bedingungen und wahrscheinliche Bedeutung dieser Erscheinung. *Zentralbl. f. Physiol.*, 1904, xviii, 457–460.

Boldireff, W. (b) Die periodische Tätigkeit des Verdauungsapparates ausser der Verdauungszeit. *Zentralbl. f. Physiol.*, 1904, xviii, 489–493.

Boldireff, W. The self-regulation of the acidity of the gastric contents and the real acidity of the gastric juice. *Quart. J. Exper. Physiol.*, 1915, viii, 1–12.

Boldireff, W. N. Bemerkungen zu den Artikeln von A. J. Carlson: Contributions to the physiology of the stomach. *Zentralbl. f. Physiol.*, 1914, xxviii, 193–194.

Boldireff, W. N. Surgical method in the physiology of digestion. Description of the most important operations on digestive system. *Ergebn. d. Physiol.*, 1925, xxiv, 399–444.

Bollman, J. L., Mann, F. C. and DePage, P. The effect of specific cholecystitis on the bile concentrating activity of the gall-bladder. *J. Lab. & Clin. Med.*, 1925, x, 544–547.

Bolton, C. and Goodhart, G. W. Duodenal regurgitation into the stomach during gastric digestion. *Lancet*, 1922, i, 420–425.

Bönniger, M. Zur Diagnose des Ulcus Ventriculi. *Berl. klin. Wchnschr.*, 1908, xlv, 396–398.

Borchers, E. (a) Die Aussichten der Behandlung von Motilitätsstörungen des Magens durch Vagusunterbrechung. *Deutsche. Ztschr. f. Chir.*, 1921, clxii, 19–28.

Borchers, E. (b) Anteil des Nervus vagus an der motorischen Innervation des Magens im Hinblick auf die operative Therapie von Magenkrankheiten: Studien zur Physiologie und Pathologie der Magenbewegungen, sowie zu modernen Problemen der Magenchirurgie. *Beitr. z. klin. Chir.*, 1921, cxxii, 547–622.

Borchers, E. Ueber die Resektion der kleinen Kurvatur und deren Folgen für Magenform und Motilität. *Arch. f. klin. Chir.*, 1922, cxxii, 198–217.

Borgbjärg, A. Verzögerung der Magenentleerung bei Darmkrankheiten. *Archiv. f. Verdauungskr.*, 1911, xvii, 706–721.

Boring, E. G. The sensations of the alimentary canal. *Am. J. Psychol.*, 1915, xxvi, 1–57.

Bose, J. C. Researches on the Irritability of Plants. London, 1913.

Bottazzi, F. Contributions to the physiology of unstriated muscular tissue. Part iv. The action of electrical stimuli upon the oesophagus of Aplysia Depilans and Aplysia Limacina. *J. Physiol.*, 1898, xxii, 481–506.

Bottazzi, F. (a) Untersuchungen über das viscerale Nervensystem der decapoden Crustacean. *Ztschr. f. Biol.*, 1902, xliii, 341–371.

Bottazzi, F. (b) Untersuchungen über das viscerale Nervensystem der Selachier. *Ztschr. f. Biol.*, 1902, xliii, 372–442.

Bottazzi, F. and Grünbaum, O. F. F. On plain muscle. *J. Physiol.*, 1899, xxiv, 51–71.

Bowditch, H. P. Movements of the alimentary canal. *Science*, 1897, v, 901–902.

Boycott, A. E. Observations on the gaseous metabolism of the small intestine of the rabbit. *J. Physiol.*, 1905, xxxii, 343–357.

Boycott, A. E. and Damant, G. C. C. Note on the quantities of marsh-gas, hydrogen, and carbon dioxide produced in the alimentary canal of goats. *J. Physiol.*, 1907, xxxvi, 283–287.

Boyd, W. Studies in gall-bladder pathology. *Brit. J. Surg.*, 1923, x, 337–356.

Boyden, E. A. The gall-bladder in the cat; its development, its functional periodicity, and its anatomical variation as recorded in 2500 specimens. *Anat. Record*, 1923, xxiv, 388–389.

Boyden, E. A. The effect of natural foods on the distention of the gall-bladder, with a note on the change in pattern of the mucosa as it passes from distention to collapse. *Anat. Record*, 1925, xxx, 333–364.

Boyden, E. A. (a) A study of the behavior of the human gall-bladder in response to the ingestion of food; together with some observations on the mechanism of the expulsion of bile in experimental animals. *Anat. Record*, 1926, xxxiii, 201–255.

Boyden, E. A. (b) Behavior of human gall-bladder during fasting and in response to food. *Proc. Soc. Exper. Biol. & Med.*, 1926, xxiv, 157–162.

Brandl, J. and Tappeiner, H. Versuche über Peristaltik nach Abführmitteln. *Arch. f. exper. Path. u. Pharmakol.*, 1890, xxvi, 177–185.

Brandt, W. Die Innervation des Magens. *Ztschr. f. ang. Anat.*, 1920, v, 302–326.

Brewer, G. E. Some observations upon the surgical anatomy of the gall-bladder and ducts. *Johns Hopkins Hosp. Rep.*, 1900, ix, 337–354.

Brinton, W. The Diseases of the Stomach. London, 1859.

Brown, G. L. and M'Swiney, B. A. Reaction to drugs of strips of the rabbit's gastric musculature. *J. Physiol.*, 1926, lxi, 261.

Brücke, E. von. Zur Physiologie der Kropfmusculatur von Aplysia Depilans. *Arch. f. d. ges. Physiol.*, 1905, cviii, 192–215.

Brücke, E. von. Versuche an ausgeschnittenen und nach einer Drehung um 180° reimplantierten Flimmerschleimhaut Stücken. *Arch. f. d. ges. Physiol.*, 1916, clxvi, 45–54.

Brunemeier, E. H. and Carlson, A. J. Contributions to the physiology of the stomach. xix. Reflexes from the intestinal mucosa to the stomach. *Am. J. Physiol.*, 1915, xxxvi, 191–195.

Bryant, J. Observations upon the growth and length of the human intestine. *Am. J. M. Sc.*, 1924, clxvii, 499–520.

Buchanan, F. Dissociation of auricles and ventricles in hibernating dormice. *J. Physiol.*, 1911, xlii, 19–20.

Budde, W. and Gelhorn, E. Beiträge zur Physiologie der Magenmuskulatur. ii. Mitteilung. *Arch. f. d. ges. Physiol.*, 1924, cciii, 170–185.

Bunch, J. L. On the origin, course and cell-connections of the visceromotor nerves of the small intestine. *J. Physiol.*, 1898, xxii, 357–379.

Burden, V. G. Observations on the histologic and pathologic anatomy of the hepatic, cystic, and common bile ducts. *Ann. Surg.*, 1925, lxxxii, 584–597; *Collect. Papers Mayo Clinic*, 1925, xvii, 107–121.

Burget, G. E. The regulation of the flow of bile. *Am. J. Physiol.*, 1925, lxxiv, 583–589.

Burget, G. E. The regulation of the flow of bile. ii. Effect of eliminating the sphincter of Oddi. *Am. J. Physiol.*, 1926, lxxix, 130–134.

Burnett, F. L. Fecal units and intestinal rate, a basis for the study of health and intestinal indigestion. *Boston M. & S. J.*, 1921, clxxxiv, 371–376; 415–422.

Burnett, F. L. The intestinal rate and the form of the feces. *Am. J. Roentgenol.*, 1923, x, 599–604.

Burnham, M. P. Indirect roentgen findings in chronic infection of the biliary ducts and gallbladder. *Am. J. Roentgenol.*, 1923, x, 105–112.

Burrows, M. T. Rhythmical activity of isolated heart muscle cells in vitro. *Science*, 1912, xxxvi, 90–92.

Busch, W. Beitrag zur Physiologie der Verdauungsorgane. *Virchow's Arch. f. path. Anat.*, 1858, xiv, 140–186.

Butsch, J. L. Ulcers of the gastro-intestinal tract with special reference to gastro-jejunal ulcers. *Papers from the Mayo Foundation and the Medical School of the University of Minnesota*, 1915–1920, i, 57–84.

Caballero, R. V. Etude expérimentale de la déglutition oesophagienne. Excitabilité de l'oesophage et arrêt épicardiaque. *Compt. rend. Soc. de biol.*, 1924, lxxvi, 927–930.

Calugareanu, D. Die Darmatmung von Cobitis fossilis. i. Mitt. Über den Bau des Mitteldarms. *Arch. f. d. ges. Physiol.*, 1907, cxviii, 42–51. ii. Mitt. Über den Gaswechsel. *Ibid.*, 1907, cxx, 425–450.

Campbell, H. F. Rectal alimentation in the nausea and inanition of pregnancy. Intestinal inhaustion, an important factor and the true solution of its efficiency. *Tr. Am. Gynec. Soc.*, 1878, iii, 268–298.

Cannon, W. B. (a) The movements of the stomach, studied by means of the roentgen rays. *Am. J. Physiol.*, 1898, i, Proc. xiii–xiv.

Cannon, W. B. (b) The movements of the stomach studied by means of the roentgen rays. *Am. J. Physiol.*, 1898, i, 359–382.

Cannon, W. B. The movements of the intestines studied by means of the roentgen rays. *Am. J. Physiol.*, 1902, vi, 251–277.

Cannon, W. B. The passage of different foodstuffs from the stomach and through the small intestines. *Am. J. Physiol.*, 1904, xii, 387–418.

Cannon, W. B. Auscultation of the rhythmic sounds produced by the stomach and intestines. *Am. J. Physiol.*, 1905, xiv, 339–353.

Cannon, W. B. (a) The motor activities of the stomach and small intestine after splanchnic and vagus section. *Am. J. Physiol.*, 1906, xvii, 429–442.

Cannon, W. B. (b) Recent advances in the physiology of the digestive organs bearing on medicine and surgery. *Am. J. M. Sc.*, 1906, cxxxi, 563–578.

Cannon, W. B. The acid control of the pylorus. *Am. J. Physiol.*, 1907, xx, 283–322.

Cannon, W. B. Further observations on the myenteric reflex. *Am. J. Physiol.*, 1908, xxiii, 26–27.

Cannon, W. B. The influence of emotional states on the functions of the alimentary canal. *Am. J. M. Sc.*, 1909, cxxxvii, 480–487.

Cannon, W. B. (a) The Mechanical Factors of Digestion. New York, 1911.

Cannon, W. B. (b) The importance of tonus for the movements of the alimentary canal. *Arch. Int. Med.*, 1911, viii, 417–426.

Cannon, W. B. (c) The relation of tonus to antiperistalsis in the colon. *Am. J. Physiol.*, 1911, xxix, 238–249.

Cannon, W. B. (d) The nature of gastric peristalsis. *Am. J. Physiol.*, 1911, xxix, 250–266.

Cannon, W. B. Peristalsis, segmentation, and the myenteric reflex. *Am. J. Physiol.*, 1912, xxx, 114–128.

Cannon, W. B. Early use of the roentgen ray in the study of the alimentary canal. *J. Am. M. Assn.*, 1914, lxii, 1–3.

Cannon, W. B. and Blake, J. B. Gastro-enterostomy and pyloroplasty. *Ann. Surg.*, 1905, xli, 686–711.

Cannon, W. B. and Burket, I. R. The endurance of anemia by nerve cells in the myenteric plexus. *Am. J. Physiol.*, 1913, xxxii, 347–357.

Cannon, W. B. and Lieb, C. W. The receptive relaxation of the stomach. *Am. J. Physiol.*, 1911, xxvii, 13.

Cannon, W. B. and Moser, A. The movements of the food in the esophagus. *Am. J. Physiol.*, 1898, i, 435–444.

Cannon, W. B. and Murphy, F. T. The movements of the stomach and intestines in some surgical conditions. *Ann. Surg.*, 1906, xliii, 512–536.

Cannon, W. B. and Washburn, A. L. An explanation of hunger. *Am. J. Physiol.*, 1912, xxix, 441–454.

Carey, E. J. Studies on the anatomy and muscular action of the small intestine. *Internat. J. Gastro-Enter.*, 1921, i, 1–10.

Carlson, A. J. Physiology of the ventral nerve cord of myriapoda. *J. Exper. Zoöl.*, 1904, i, 269–287.

Carlson, A. J. Contributions to the physiology of the stomach. v. The influence of stimulation of the gastric mucosa on the contractions of the empty stomach (hunger contractions) in man. *Am. J. Physiol.*, 1913, xxxii, 245–263.

Carlson, A. J. The Control of Hunger in Health and Disease. Chicago, 1916.

Carlson, A. J. Contributions to the physiology of the stomach. xliv. The origin of the epigastric pains in cases of gastric and duodenal ulcer. *Am. J. Physiol.*, 1917, xlv, 81–91.

Carlson, A. J. Studies on the visceral sensory nervous system. xiii. The innervation of the cardia and the lower end of the esophagus in mammals. *Am. J. Physiol.*, 1922, lxi, 14–41.

Carlson, A. J. Physiology of the liver. Present status of our knowledge. *J. Am. M. Assn.*, 1925, lxxxv, 1468–1472.

Carlson, A. J. Antiperistalsis in the upper third of the esophagus in man. *Proc. Soc. Exper. Biol. & Med.*, 1926, xxiii, 771–773.

Carlson, A. J., Boyd, T. E. and Pearcy, J. F. Studies on the visceral sensory nervous system. *Arch. Int. Med.*, 1922, xxx, 409–433.

Carlson, A. J., Boyd, T. E., and Pearcy, J. F. Studies on the visceral sensory nervous system. xiii. The innervation of the cardia and the lower end of the esophagus in mammals. *Am. J. Physiol.*, 1922, lxi, 14–41.

Carlson, A. J. and Braafladt, L. H. Contributions to the physiology of the stomach. xviii. On the sensibility of the gastric mucosa. *Am. J. Physiol.*, 1915, xxxvi, 153–170.

Carlson, A. J. and Litt, S. Studies on the visceral nervous system. On the reflex control of the pylorus. *Arch. Int. Med.*, 1924, xxxiii, 281–291.

Carlson, A. J., Van de Erve, J., Lewis, J. H. and Orr, S. J. Contributions to the physiology of the stomach. xvi. The action of the so-called stomachics or bitters on the hunger mechanism. *J. Pharmacol. & Exper. Therap.*, 1914, vi, 209–218.

Carlson, A. J. and Meek, W. J. On the mechanism of the embryonic heart rhythm in Limulus. *Am. J. Physiol.*, 1908, xxi, 1–10.

Carman, R. D. The Roentgen Diagnosis of Diseases of the Alimentary Canal. Philadelphia, 1920.

Carnot, P. Le jeu du sphincter pylorique. *Arch. d. mal. de l'appar. digest.*, 1907, i, 651–666.

Carnot, P. Les mouvements de l'estomac et du duodenum études par la méthode de la perfusion. *Compt. rend. Soc. de Biol.*, 1913, lxxiv, 1265–1268.

Carnot, P. and Chassevant, A. (a) Modifications subies dans l'estomac et le duodenum par les solutions salines suivant leur concentration moléculaire. Le reflex Δ regulateur du sphincter pylorique. *Compt. rend. Soc. de biol.*, 1905, lviii, 173–176.

Carnot, P. and Chassevant, A. (b) Sur le passage pylorique des solutions de glucose. *Compt. rend. Soc. de biol.*, 1905, lviii, 1069–1072.

Carnot, P. and Chassevant, A. (c) Des modifications subies dans l'estomac et le duodenum par les solutions acides ingérées. *Compt. rend. Soc. de biol.*, 1905, lix, 106–109.

Carnot, P. and Glenard, R. Sur la technique de la perfusion intestinale. Facteurs mecaniques influencant la vitesse de la perfusion intestinale. *Compt. rend. Soc. de Biol.*, 1912, lxxii, 496–499, 661–664.

Carnot, P. and Glenard, R. De la perfusion intestinale chez l'animal vivant. *Compt. rend. Soc. de Biol.*, 1913, lxxiv, 328–331.

Carpenter, F. W. and Conel, J. L. A study of ganglion cells in the sympathetic nervous system, with special reference to intrinsic sensory neurons. *J. Comp. Neurol.*, 1914, xxiv, 269–281.

Cary, R. J. Digestion: A historical survey. *Johns Hopkins Hosp. Bull.*, 1916, xxvii, 142–152.

Case, J. T. (a) A critical study of intestinal stasis with new observations respecting the causes of ileal stasis. *Arch. Roentg. Ray*, 1914, xix, 45–52.

Case, J. T. (b) X-ray observations on colonic peristalsis and antiperistalsis with special reference to the function of the ileocolic valve. *Proc. 17th Internat. Congr. Med.*, 1914, Sec. 22, Radiology, Pt. 2, 11–41; *Med. Record*, 1914, lxxxv, 415–427.

Case, J. T. (a) Basic considerations in the roentgen study of intestinal stasis. *Penn. M. J.*, 1915, xviii, 683–704.

Case, J. T. (b) Discussion on a paper by L. T. Swaim. *Penn. M. J.*, 1915, xviii, 724.

Case, J. T. (c) The *x*-ray investigation of the colon. *Arch. Roentg. Ray*, 1915, xix, 375–387.

Case, J. T. Roentgen observations on the duodenum with special reference to lesions beyond the first portion. *Am. J. Roentgenol.*, 1916, iii, 314–326.

Case, J. T. Gastric and duodenal roentgen-ray findings after operation. *J. Am. M. Assn.*, 1925, lxxxv, 1385–1389.

Cash, J. T. Intestinal rest and movement. *Proc. Roy. Soc. Lond.*, 1886, xli, 212.

Chase, M. R. An experimental study of the vagus nerve. *J. Comp. Neurol.*, 1916, xxvi, 421–428.

Child, C. M. Studies on the dynamics of morphogenesis and inheritance in experimental reproduction. vii. The stimulation of pieces by section in planaria dorotocephala. *J. Exper. Zoöl.*, 1914, xvi, 413–441.

Child, C. M. Senescence and Rejuvenescence. Chicago, 1915.

Child, C. M. The gradient in susceptibility to cyanides in the meridional conducting path of the Ctenophore mnemiopsis. *Am. J. Physiol.*, 1917, xliii, 87–112.

Child, C. M. Some considerations concerning the nature and origin of physiological gradients. *Biol. Bull.*, 1920, xxxix, 147–187.

Chiray, M. and Pavel, i. Physiology of the Meltzer-Lyon test. *Am. J. M. Sc.*, 1926, clxxii, 11–21.

Chlumskij, Uber die Gastroenterostomie. *Beitr. z. klin. Chir.*, 1898, xx, 487–544.

Clark, G. A. Deglutition apnoea. *J. Physiol.*, 1921, liv, Proc. Physiol. Soc., lix.

Clopton, M. B. and Mills, R. W. Gastric motility after pyloric obstruction in infancy. *Am. J. Dis. Child.*, 1922, xxiv, 404–412.

Cohn, M. Röntgenuntersuchung einer Frau, welcher der Magen und beide Nervi vagi reseziert worden sind. *Berl. klin. Wchnschr.*, 1913, l, 1393–1395.

Cohnheim, O. Beobachtungen über Magenverdauung. *München. med. Wchnschr.*, 1907, liv, 2581–2583.

Cohnheim, O. Die Physiologie der Verdauung und Ernährung. Berlin, 1908.

Cohnheim, O. and Best, F. Über Bewegungsreflexe des Magendarmkanals. *München. med. Wchnschr.*, 1910, lvii, 1858–1860.

Cohnheim, O. and Dreyfus, G. L. (a) Zur Physiologie und Pathologie der Magenverdauung. *München med. Wchnschr.*, 1908, lv, 2484–2485.

Cohnheim, O. and Dreyfus, G. L. (b) Zur Physiologie und Pathologie der Magenverdauung. *Ztschr. f. physiol. Chemie*, 1908, lviii, 50–83.

Colasanti, G. Über den Einfluss der umgebenden Temperatur auf den Stoffwechsel der Warmblüter. *Arch. f. d. ges. Physiol.*, 1877, xiv, 92–124.

Cole, L. G. The complex motor phenomena of various types of unobstructed gastric peristalsis. *Arch. Roentg. Ray*, 1911, xvi, 242–247.

Cole, L. G. Physiology of the pylorus, pilleus ventriculi and duodenum as observed roentgenographically. *J. Am. M. Assn.*, 1913, lxi, 762–766.

Cole, L. G. Relation of lesions of the small intestine to disorders of the stomach and cap as observed roentgenologically. *Am. J. M. Sc.*, 1914, cxlviii, 92–118.

Cole, L. G. Motor phenomena of the stomach, pylorus and cap observed roentgenographically. *Am. J. Physiol.*, 1917, xlii, 618–619.

Cole, W. H. Relation of gastric content to the physiology of the common duct sphincter. *Am. J. Physiol.*, 1925, lxxii, 39–42.

Copher, G. H. Cholecystography. Appearance and disappearance of the shadow. *J. Am. M. Assn.*, 1925, lxxxiv, 1563–1564.

Copher, G. H. and Kodama, S. The regulation of the flow of bile and pancreatic juice into the duodenum. *Arch. Int. Med.*, 1926, xxxviii, 647–653.

Courtade, D. and Guyon, J. F. Influence motrice du grand sympathique sur l'intestin grêle. *Arch. d. Physiol.*, 1897, ix, 422–433.

Courtade, D. and Guyon, J. F. (a) Action motrice du pneumogastrique sur la vésicule biliaire. *Compt. rend. Soc. de biol.*, 1904, lvi, 313–316.

Courtade, D. and Guyon, J. F. (b) Le trajet des nerfs extrinséques de al vésicule biliaire. *Compt. rend. Soc. de biol.*, 1904, lvi, 874–875.

Cowie, D. M. and Lyon, W. Further observations of the acid control of the pylorus in infants. *Am. J. Dis. Child.*, 1911, ii, 252–261.

Crane, A. W. American priority in the use of bismuth for the examination of the human stomach. *Am. J. Roentgenol.*, 1915, ii, 692–696.

Crohn, B. B., Reiss, J. and Radin, M. J. Experiences with the Lyon test (magnesium sulphate lavage of the duodenum). *J. Am. M. Assn.*, 1921, lxxvi, 1567–1571.

Crohn, B. B. and Wilensky, A. O. Studies in the variations of the tonus of the gastric musculature in health and disease. *Arch. Int. Med.*, 1917, xx, 145–160.

Crozier, W. J. and Pilz, G. F. Central nervous excitation by alkaloids in insects. *Am. J. Physiol.*, 1924, lxix, 41–45.

Crozier, W. J. and Stier, T. J. B. Temperature and frequency of cardiac contractions in embryos of Limulus. *J. General Physiol.*, 1927, x, 501–518.

Cullis, W. and Tribe, E. M. Distribution of nerves in the heart. *J. Physiol.*, 1913, xlvi, 141–150.

CUNNINGHAM, D. J. The varying form of the stomach in man and the anthropoid apes. *Tr. Roy. Soc. Edinb.*, 1906, xlv, 9–47.

CZYHLARZ, E. VON and SELKA, A. Das röntgenologische Verhalten des Magens bei gastrichen Krisen und beim Brechakte. *Wien. klin. Wchnschr.*, 1913, xxvi, 842–843.

DAGAEW, W. F. Aenderungen in den Verdauungsprozessen nach Gastroduodenostomie und Gastrojejunostomie und nach totaler Magenexstirpation. *Mitt. a. d. Grenzgeb. d. Med. u. Chir.*, 1913, xxvi, 176–194.

DALLA VALLE, A. Contributo alla conoscenza della forma famigliare del megacolon congenito. *Pediatria*, 1924, xxxii, 569–599.

DANIÉLOPULU, D. SIMICI, D. and DIMITRIU, C. Inscription graphique de l'intestin grêle chez l'homme. *Compt. rend. Soc. de Biol.*, 1925, xcii, 1143–1145.

DAVID, O. Röntgenologische Untersuchungen über Form und Verhalten des Dünndarms bei direkter Füllung mit Kontrastmitteln. *Mitt. a. d. Grenzgeb. d. Med. u. Chir.*, 1918, xxxi, 209–252.

DAVIS, J. E. Morphography of two hundred and eighty-five colons. *Am. J. Obst. & Gynec.*, 1916, lxxiii, 474–484.

DAY, E. C. The physiology of the nervous system of the tunicate. II. The relation of the nerve ganglion to the heart. *J. Exper. Zoöl.*, 1921, xxxiv, 45–65.

DEAVER, J. B. Appendicitis. Philadelphia, 1905.

DEKHUYZEN, M. C. A word in favor of the myogenic theory. *Quart. J. Exp. Physiol.*, 1923, Suppl. Congress Volume 100.

DELLINGER, I. P. The cilium as a key to the structure of contractile protoplasm. *J. Morphol.*, 1909, xx, 172–210.

DEMARQUAY. Recherches faites sur un malade affecte d'anus contre nature. *Union méd.*, 1874, xviii, 906–911.

DEMEL, R. Die Gefässversorgung der Speiseröhre. Ein Beitrag zur Oesophaguschirurgie. *Arch. f. klin. Chir.*, 1924, cxxviii, 453–504.

DEMUTH, F. Motilitätsprüfungen mit Eiweiss, Fett, und Kohlehydraten am kranken Magen. *Deutsches Arch. f. klin. Med.*, 1921, cxxxvii, 292–298.

DENDY, W. C. Discovery of a large egg-cup in the ileum of a man. *Lancet*, 1834, i, 675–677.

DEVINE, H. B. Basic principles and supreme difficulties in gastric surgery. *Surg., Gynec. & Obst.*, 1925, xl, 1–16.

DIAMOND, J. S. An experimental study of the Meltzer-Lyon test, with comment on the physiology of the gall-bladder and sphincter vateri. *Am. J. M. Sc.*, 1923, clxvi, 894–901.

DIETERLEN, F. Über das Aufwärtswandern der Bakterien im Verdauungskanal und seine Bedeutung für die Infektion des Respirationstraktus. *Zentralbl. f. Bakteriol.*, 1907, lxv, 385–387.

DIETLEN, H. Die Insuffizienz der Valvula ileocoecalis im Röntgenbild. *Fortschr. a. d. Geb. d. Röntgenstrahlen.*, 1914, xxi, 23–30.

DISSE, Über die Blutgefässe der menschlichen Magenschleimhaut, besonders über die Arterien derselben. *Arch. f. Mikr. Anat.*, 1904, lxiii, 512–531.

Dittler, R. Über den Erregungsablauf am Kropfe der Aplysia. *Arch. f. d. ges. Physiol.*, 1911, cxli, 527–540.

Donaldson, A. N. Relation of constipation to intestinal intoxication. *J. Am. M. Assn.*, 1922, lxxviii, 884–888.

Doyon, M. (a) Contribution a l'étude de la contractilité des voies biliaires. Application de la méthode graphique a cette étude. *Arch. de physiol. norm. et path.*, 1893, v, 678–685.

Doyon, M. (b) Mouvements spontanés des voies biliaires. Caractères de la contraction de la vésicule et du canal cholédoque. *Arch. de physiol. norm. et path.*, 1893, v, 710–719.

Doyon, M. De l'action exercée par le système nerveux sur l'appareil excréteur de la bile. *Arch. de physiol. norm. et path.*, 1894, vi, 19–31.

Drummond, H. Observations on the functions of the colon, with special reference to the movements of enemata. *Brit. M. J.*, 1914, i, 240–242.

Ducceschi, V. Gastric studies. *Arch. per le sc. med.*, 1897, xxi, 134–137.

Dundon, J. R. Contributions to the physiology of the stomach. xliii. The influence of experimental ulcers of the stomach and duodenum on the hunger contractions of the empty stomach. *Am. J. Physiol.*, 1917, xliv, 234–238.

Dunn, A. D. and Connell, K. Report of a case of hepatoduodenostomy with some observations on the Lyon-Meltzer method of biliary drainage. *J. Am. M. Assn.*, 1921, lxxvii, 1093–1096.

Dunn, A. D. and Dunn, F. L. A method for sampling and analysis of stomach gas. *J. Lab. & Clin. M.*, 1925, x, 769–776.

Dunn, A. D. and Thompson, W. The carbon dioxide and oxygen content of stomach gas in normal persons. *Arch. Int. M.*, 1923, xxxi, 1–8.

Ecker, E. E. and Rademaekers, A. Studies on the effect of certain toxic substances in bacterial cultures on the movement of the intestines. i. The effect of soluble toxic substances of young cultures of Bac. paratyphosus B. *J. Exper. Med.*, 1926, xliii, 785–795.

Edgeworth, F. H. On a large fibred sensory supply of the thoracic and abdominal viscera. *J. Physiol.*, 1892, xiii, 260–271.

Edmunds, C. W. The point of attack of certain drugs acting on the periphery. ii. Action on the retractor penis of the dog. *J. Pharmacol. & Exper. Therap.*, 1920, xv, 201–216.

Edmunds, W. and Ballance, C. Observations and experiments on intestinal and gastrointestinal anastomosis. Med.-Chir. Tr., *Lond.*, 1896, lxxix, 255–311.

Egan, E. Azidität und Entleerung. Untersucht mittelst Dauermagensonde und Durchleuchtung. *Arch. f. Verdauungskr.*, 1915, xxi, 479–496.

Eggleston, C. Clinical observations on the emetic action of digitalis. *J. Am. M. Assn.*, 1913, lxi, 757–761.

Eggleston, C. and Hatcher, R. A. The seat of the emetic action of apomorphine. *J. Pharmacol. Exper. Therap.*, 1912, iii, 551–580.

Eggleston, C. and Hatcher, R. A. The emetic action of the digitalis bodies. *J. Am. M. Assn.*, 1913, lx, 499–503.

EGGLESTON, C. and HATCHER, R. A. The seat of the emetic action of various drugs. *J. Pharmacol. & Exper. Therap.*, 1915, vii, 225–253.

EINHORN, M. The duodenal tube as a factor in the diagnosis and treatment of gallbladder disease. *J. Am. M. Assn.*, 1916, lxvii, 1908–1910.

ELLENBERGER, W. Handbuch der vergleichenden mikroskopischen Anatomie der Haustiere. 1911, iii, 138, 174, 178.

ELLINGER, A. and PRUTZ, W. Der Einfluss von mechanischen Hindernissen im Dünndarm und Dickdarm auf die Indicanausscheidung beim Hunde. *Ztschr. f. physiol. Chem.*, 1903, xxxviii, 399–427.

ELLIOTT, T. R. On the innervation of the ileocolic sphincter. *J. Physiol.*, 1904, xxxi, 157–168.

ELLIOTT, T. R. The action of adrenalin. *J. Physiol.*, 1905, xxxii, 401–467.

ELLIOTT, T. R. The innervation of the bladder and urethra. *J. Physiol.*, 1907, xxxv, 367–445.

ELLIOTT, T. R. and BARCLAY-SMITH, E. Antiperistalsis and other muscular activities of the colon. *J. Physiol.*, 1904, xxxi, 272–304.

ELSESSER, O. J. Contribution to the physiology of the stomach. XXXI. The effect of experimental partial stenosis of the pylorus on the motility of the empty stomach. *Am. J. Physiol.*, 1916, xxxix, 303–309.

ENDERLEN and HESS. Über Antiperistaltik. *Deutsche Ztschr. f. Chir.*, 1901, lix, 240–253.

ENGELMANN, T. W. Zur Physiologie des Ureter. *Arch. f. d. ges Physiol.*, 1869, ii, 243–293.

ENGELMANN, T. W. and VAN BRAKEL, G. IV. Uber die peristaltische Bewegung, insbesondere des Darms. *Arch. f. Physiol.*, 1871, iv, 33–50.

EPPINGER, H. and HESS, L. Vagotonia: A Clinical Study in Vegetative Neurology. Translation by Kraus and Jelliffe, New York, 1917.

ESSLEMONT, J. E. Beiträge zur pharmakologischen Wirkung von Abführmittel der Aloëderivatgruppe. *Arch. f. exper. Path. u. Pharmakol.*, 1900, xliii, 274–285.

EVANS, C. L. Studies on the physiology of plain muscle. II. The oxygen usage of plain muscle and its relation to tonus. *J. Physiol.*, 1923, lviii, 22–32.

EVANS, C. L. Studies on the physiology of plain muscle. IV. The lactic acid content of plain muscle under various conditions. *Biochem. J.*, 1925, xix, 1115–1127.

EVANS, C. L. The physiology of plain muscle. *Physiol. Rev.*, 1926, vi, 358–398.

EVANS, C. L. and UNDERHILL, S. W. F. Studies on the physiology of plain muscle. *J. Physiol.*, 1923, lviii, 1–14.

EWALD, C. A. Lectures on Diseases of the Digestive Organs. Translation from Ed. 3. of 1890 by Saundby. New Syd. Soc., London, 1891.

EWALD, C. A. Über ein wenig beachtetes Frühsymptom des Ileus. *Berl. klin. Wchnschr.*, 1907, xliv, 1416–1417.

EWALD, C. A. AND BOAS, J. Beiträge zur Physiologie und Pathologie der Verdauung. *Virchow's Arch. f. path. Anat.*, 1885, ci, 325–375; 1886, civ, 271–305.

EXNER, A. Wie schützt sich der Verdauungstract vor Verletzungen durch spitze Fremdkörper? *Arch. f. d. ges. Physiol.*, 1902, lxxxix, 253–280.

Exner, A. and Schwarzmann, E. Gastrische Krisen und Vagotomie. *Mitt. a. d. Grenzgeb. d. Med. u. Chir.*, 1914, xxviii, 15–52.

Eykman, P. H. Der Schlingact dargestellt nach Bewegungsphotographien mittelst Röntgenstrahlen. *Arch. f. d. ges. Physiol.*, 1903, xcix, 513–571.

Eyster, J. A. E. and Meek, W. J. Experiments on the origin and propagation of the impulse in the heart. *Heart*, 1914, v, 119–134.

Farr, R. E. Abdominal surgery under local anesthesia. *J. Am. M. Assn.*, 1919, lxxiii, 391–395.

Farrell, J. I. and Ivy, A. C. Studies on the motility of the transplanted gastric pouch. *Am. J. Physiol.*, 1926, lxxvi, 227.

Faulhaber, M. and von Redwitz, E. F. Über den Einfluss der "circulären Magenresektion" auf die Sekretion und Motilität des Magens. *Med. Klin.*, 1914, x, 680–684.

Faulhaber, M. and von Redwitz, E. F. Zur Klinik und Behandlung des "pylorusfernen" Ulcus ventriculi. *Mitt. a. d. Grenzgeb. d. Med. u. Chir.*, 1915, xxviii, 150–212.

Fermi, C. (a) Über die Verdaulichkeit der Speisen im Magen in Beziehung zur Hygiene. *Arch. f. Physiol.*, 1901, Suppl. 1–83.

Fermi, C. (b) Ueber das Kauen der Speisen. *Arch. f. Physiol.*, 1901, Suppl., 98–108.

Finkenheim, F. Über die operative Behandlung der steinlosen Gallenkoliken. *Zentralbl. f. Chir.*, 1924, li, 1608–1618.

Finney, J. M. T. and Friedenwald, J. Thirteen years' experience with pyloroplasty. *Surg., Gynec. and Obst.*, 1914, xviii, 273–284.

Fischer, H. Ueber funktionelle Anpassung am Fledermausmagen. *Arch. f. d. ges. Physiol.*, 1909, cxxix, 113–137.

Fischer, H. G. Histological structure of the retractor penis muscle of the dog. *Anat. Record*, 1917, xiii, 69–79.

Fitz, R. and Aldrich, M. Clinical observations on certain constituents of the bile. *J. Am. M. Assn.*, 1922, lxxix, 2129–2132.

Fitzgibbon, J. H. Reverse peristalsis associated with nausea. *J. Am. M. Assn.*, 1925, lxxxv, 1889–1890.

Fletcher, W. M. Preliminary note on the motor and inhibitor nerve-endings in smooth muscle. *J. Physiol.*, 1898, xxii, 37–40.

Flint, A. A Textbook of Human Physiology. Ed. 4, New York, 1895.

Flöel, O. Die Wirkung der Kalium- und Natrium-Salze auf die glatte Muskulatur verschiedener Thiere. *Arch. f. d. ges. Physiol.*, 1885, xxxv, 157–173.

Forbes, A. and Gregg, A. ii. The correlation between strength of stimuli and the direct and reflex nerve response. *Am. J. Physiol.*, 1915, xxxix, 172–235.

Frankl-Hochwart, L. von, and Fröhlich, A. Über Tonus und Innervation der Sphinkteren des Anus. *Arch. f. d. ges. Physiol.*, 1900, lxxxi, 420–482.

Fredet, P. (Rapport au VIe Congress de gynecologie, d'obstetrique et de pediatrie, Sept., 1910) La stenose du pylore par hypertrophie musculaire chez les nourrissons. *Bull. et mém. Soc. de chir. de Paris*, 1921, xlvii, 451–470.

FREESE, J. A. The force and contraction of the gall bladder in the course of its motor and inhibitory nerve fibers. *Johns Hopkins Hosp. Bull.*, 1905, xvi, 235–237.

FRIEDLÄNDER, B. Über das Kriechen der Regenwürmer. *Biol. Centralbl.* 1888, viii, 363–366.

FRIES, J. A. Combustible gases escaping from an animal. *Proc. 23rd Annual Meeting of Soc. Promotion Agric. Sc.*, 1902, 110–118.

FRIES, J. A. Intestinal gases of man. *Am. J. Physiol.*, 1906, xvi, 468–474.

FRIES, J. A. The respiratory quotient and its uncertainty. *Am. J. Physiol.*, 1921, lv, 53–64.

FRÖHLICH, A. and MEYER, H. H. Die sensible Innervation von Darm und Harnblase. *Wien. klin. Wchnschr.*, 1912, xxv, 29–30.

FUBINI, S. Einfluss der Elektrischen Inductionsströme, des Kochsalzes und der Tinctura opii crocata auf die Geschwindigkeit der Bewegungen des Dünndarms. *Centralbl. f. d. med. Wissensch.*, 1882, xxvi, 579–581.

GAGE, S. H. The ampulla of Vater and the pancreatic ducts in the domestic cat (Felis domestica). *Am. Quart. Micr. J.*, 1879, i, 123–131; 169–180.

GARREY, W. E. The temperature coefficient of the neurogenic rhythm of the heart of Limulus Polyphenus. *J. Physiol.*, 1920, iii, 41–48.

GASKELL, J. F. Adrenalin in annelids. A contribution to the comparative study of the origin of the sympathetic and the adrenalin-secreting systems and of the vascular muscles which they regulate. *J. General Physiol.*, 1919, ii, 73–85.

GASKELL, W. H. On the innervation of the heart, with especial reference to the heart of the tortoise. *J. Physiol.*, 1883, iv, 43–127.

GASKELL, W. H. The Contraction of Cardiac Muscle. Schaefer's Textbook of Physiology. Edinburgh and London, 1900, ii, 169–227.

GASKELL, W. H. The Involuntary Nervous System. London, 1916.

GAULT, C. C. The physiology of the atrio-ventricular connection in the turtle. III. The influence of the vagi and of the sympathetic nerves on its rhythm-forming power. *Am. J. Physiol.*, 1917, xliii, 22–42.

GAYDA, T. Beiträge zur Physiologie das überlebenden Dünndarms von Säugetieren. *Arch. f. d. ges. Physiol.*, 1913, cli, 407–455.

GEHUCHTEN, A. VON. Recherches histologiques sur l'appareil digestif de la larve de la Ptychoptera Contaminata. *Cellule*, 1890, vi, 183–292.

GELLHORN, E. and BUDDE, W. Beiträge zur Physiologie der Magenmuskulatur. I. Mitteilung: Studien am überlebenden Magen des Frosches. *Arch. f. d. ges. Physiol.*, 1923, cc, 604–619.

GERLACH, L. Über den Auerbachschen Plexus myentericus. *Ber. ü. d. Verhandl. d. k. sächs. Gesellsch. d. Wissensch.*, Leipz., math.-phys. Klasse, 1873, xxv, 1–10.

GEROULD, J. H. Periodic reversal in direction of heart beat in the chrysalis of Colias. *Anat. Record*, 1924, xxix, 90.

GILMER. Effects of good or bad taste of the contrast meal. *Zentralbl. f. Röntgenstrahlen*, 1911, ii, 235, Abstract.

Ginsburg, H. and Tumpowsky, I. Contributions to the physiology of the stomach. l. Studies on the control of hunger by drugs. *Arch. Int. Med.*, 1918, xxii, 553–570.

Ginsburg, H., Tumpowsky, I. and Hamburger, W. W. Contributions to the physiology of the stomach. xxxv. The newer interpretation of the gastric pain in chronic ulcer. *J. Am. M. Assn.*, 1916, lxvii, 990–994.

Glaister, J. and Logan, D. D. Gas Poisoning in Mining and other Industries. Edinburgh, 1914.

Glassner K. Experimentelles über die Obstipation. *Wien. klin. Wchnschr.*, 1904, xvii, 1205–1206.

Glenard, R. Les mouvements de l'intestin en circulation artificielle. *Arch. d mal. de l'appar. digest.*, 1915, viii, 61–95.

Gold, H. and Hatcher, R. A. Studies on vomiting. *J. Pharmacol. & Exper. Therap.*, 1926, xxviii, 209–218.

Goltz, F. Ueber die Funktionen des Lendenmarks des Hundes. *Arch. f. d. ges. Physiol.*, 1874, viii, 460–498.

Goltz, F. and Ewald, J. R. Der Hund mit verkürztem Rückenmark. (Nach gemeinschaftlich angestellten Beobachtungen.) *Arch. f. d. ges. Physiol.*, 1896, lxiii, 362–400.

Goodall, J. S. The contraction of the isolated esophagus of the cat. *J. Physiol.*, 1905, xxxiii, i–ii.

Graham, E. A. New developments in our knowledge of the gallbladder. *Am. J. M. Sc.*, 1926, clxxii, 625–643.

Graham, E. A. and Cole, W. H. Roentgenologic examination of the gallbladder: Preliminary report of a new method utilizing the intravenous injection of tetrabromphthalein. *J. Am. M. Assn.*, 1924, lxxxii, 613–614.

Graham, E. A., Cole, W. H. and Copher, G. H. (a) Roentgenological visualization of the gallbladder by the intravenous injection of tetrabromphenolphthalein. *Ann. Surg.*, 1924, lxxx, 473–477.

Graham, E. A., Cole, W. H. and Copher, G. H. (b) Visualization of the gallbladder by the sodium salt of tetrabromphenolphthalein. *J. Am. M. Assn.*, 1924, lxxxii, 1777–1778.

Graham, E. A., Cole, W. H. and Copher, G. H. Cholecystography: an experimental and clinical study. *Ann. Surg.*, 1925, lxxxiv, 14–16.

Graves, R. C. and Davidoff, L. M. Studies on ureter and bladder with especial reference to regurgitation of vesical contents. *J. Urol.*, 1923, x, 185–231.

Gray, J. The mechanism of ciliary movement. *Proc. Roy. Soc.*, Lond., Ser. B. 1922, xciii, 104–121.

Greene, C. W. and Gilbert, N. C. ii. The electrocardiogram during extreme oxygen-want. *Am. J. Physiol.*, 1920, li, 181.; also lvi, 475–486.

Groedel, F. M. Die Magenbewegungen. Hamburg, 1912.

Groedel. F. M. Die Eigenbewegung des Magens im Röntgenbild. *Fortschr. a. d. Geb. d. Röntgenstrahlen.*, 1925, xxxiii, 8–15.

Grützner, P. Zur Physiologie der Darmbewegung. *Deutsche med. Wchnschr.*, 1894, xx, 897–898.

Grützner, P. Über die Bewegungen des Darminhaltes. *Arch. f. d. ges. Physiol.*, 1898, lxxi, 492–522.

Grützner, P. Die glatten Muskeln. *Ergebn. d. Physiol.*, 1904, iii, Part 2, 12–88.

Grützner, P. Ein Beitrag zum Mechanismus der Magenverdauung. *Arch. f. d. ges. Physiol.*, 1905, cvi, 463–522.

Gubaroff, A. von. Über den Verschluss des menschlichen Magens an der Cardia. *Arch. f. Anat.* 1886, 395–402.

Guinard, L. Sur l'état nauséeux et les vomissements provoquées par la morphine. *Lyon méd.*, 1895, lxxx, 37–49.

Gunn, J. A. and Underhill, S. W. F. Experiments on the surviving mammalian intestine. *Quart. J. Physiol.*, 1914, viii, 275–296.

Gustafson, F. G. Hydrogen-ion concentration gradient in plants. *Physiol. Abstr.*, 1924, ix, 191.

Haane, G. Über die Cardiadrüsen und die Cardiadrüsenzone des Magens der Haussäugethiere, *Arch. f. Anat.* 1905, 1–32.

Haberer, H. von. Ulcus pepticum jejuni. *Arch. f. Verdauungskr.*, 1921, xxviii, 1–28.

Haberer, H. von. Ulcus ventriculi, Ulcus duodeni, Ulcus pepticum jejuni, mit besonderer Berücksichtigung der chiurgischen Therapie. *Deutsche. Ztschr. f. Chir.*, 1922, clxxii, 1–77.

Haffter, W. Neue Versuche über den Nervus splanchnicus major. *Henle u. Pfeufer, Ztschr. f. rationelle Med.*, 1854, iv, 322–329.

Haggard, H. W. The toxicology of hydrogen sulphide. *J. Indust. Hyg.*, 1925, vii, 113–121.

Hall, F. G. The swim-bladder of fishes. *Biol. Bull.*, 1924, xlvii, 79–126.

Hall, M. Diaperistaltic and antiperistaltic action. *Lancet*, 1857, i, 82–83.

Haller, A. von. First Lines of Physiology. 1st Am. Ed., Troy, N. Y.

Halperin, G. The pathogenesis of gastro-duodenal ulcer. *Surg., Gynec. & Obst.*, 1926, xliii; *Internat. Abstract. of Surg.* 173–180.

Halsey, J. T. The digitalized dog's heart as affected by amyl nitrite or atropine, studied electrocardiographically. *J. Exper. M.*, 1917, xxv, 729–754.

Hammett, F. S. The intestinal mechanism primarily stimulated by sodium carbonate (albino rat). *Am. J. Physiol.*, 1921, lv, 414–421.

Hamrick, R. A. The emptying of the gall bladder: an experimental study. *Am. J. M. Sc.*, 1927, clxxiv, 168–180.

Hannes, B. Über die Insuffizienz der Valvula ileocecalis. *München. med. Wchnschr.*, 1920, lxvii, 745–746.

Hardt, L. L. J. Pain in active pathologic processes in stomach or duodenum. Gastric and duodenal contractions as the direct cause. *J. Am. M. Assn.*, 1918, lxx, 837–839.

Hardt, L. L. J. Studies of the cause of pain in gastric and duodenal ulcers: ii. Peristalsis as direct cause of pain in gastric ulcers with achylia and in duodenal ulcers. *Arch. Int. Med.*, 1922, xxix, 684–689.

Harer, W. B., Hargis, E. H. and Van Meter, W. C. Studies of the function of the gallbladder. *Surg., Gynec. & Obst.*, 1922, xxxiv, 307–320.

Hart, T. S. Paroxysmal tachycardia. *Heart*, 1912, iv, 128–136.

Hartman, H. R. Blood changes in a gastrectomized patient simulating those in pernicious anemia. *Am. J. M. Sc.*, 1921, clxii, 201–206.

Hastings, A. B., Neill, J. M., Morgan, H. J. and Binger, C. A. L. Blood reaction and blood gases in pneumonia. *J. Clin. Invest.*, 1924, i, 25–45.

Hatcher, R. A. The mechanism of vomiting. *Physiol. Rev.*, 1924, iv, 479–504.

Hatcher, R. A. and Eggleston, C. The emetic action of the digitalis bodies. *J. Pharmacol. & Exper. Therap.*, 1912, iv, 113–134.

Hatcher, R. A. and Weiss, S. Further observations on the seat of the emetic action of the digitalis bodies. *Proc. Soc. Exper. Biol. & Med.*, 1921, xix, 7–8.

Hatcher, R. A. and Weiss, S. The seat of the emetic action of the digitalis bodies. *Arch. Int. Med.*, 1922, xxix, 690–704.

Hatcher, R. A. and Weiss, S. Studies on vomiting. *J. Pharmacol. & Exper. Therap.*, 1923, xxii, 139–193.

Haudek, M. Ueber die diagnostische Verwertbarkeit der Antiperistaltik des Magens. *Wien. klin. Wchnschr.*, 1912, lxii, 1059–1064; *Arch. Roentg. Ray*, 1913, xvii, 312–317.

Haudek, M. and Stigler, R. Radiologische Untersuchungen über den Zusammenhang zwischen Austreibungszeit des normalen Magens und Hungergefühl. *Arch. f. d. ges. Physiol.*, 1910, cxxxiii, 145–160.

Hawk, P. B., Rehfuss, M. E. and Bergeim, O. The response of the normal human stomach to the various standard foods and a summary. *Am. J. M. Sc.*, 1926, clxxi, 359–369.

Head, H. On disturbances of sensation with especial reference to the pain of visceral disease. *Brain*, 1894, xvii, 339–480.

Hecht, S. The physiology of the blood system of Ascidia Atra Lenseur. *Am. J. Physiol.*, 1918, xlv, 157–187.

Hedblom, C. A. and Cannon, W. B. Some conditions affecting the discharge of food from the stomach. *Am. J. M. Sc.*, 1909, cviii, 504–521.

Heile, B. Experimentelle Beobachtungen über die Resorption im Dünn-und Dickdarm. *Mitt. a. d. Grenzgeb. d. Med. u. Chir.*, 1905, xiv, 474–486.

Heineke, D. and Selms, M. Van. De la sensibilité de l'éstomac. *Arch. d. mal. d. l'appar. digest*, 1908, ii, 467–482.

Helly, K. K. Beitrag zur Anatomie des Pankreas und seiner Ausführungsgänge. *Arch. f. Mikr. Anat.*, 1898, lii, 773–793.

Henderson, W. F. Duodenal antiperistalsis. *J. Am. M. Assn*, 1925, lxxxv, 1462–1465.

Hendrickson, W. F. A study of the musculature of the entire extra-hepatic biliary system, including that of the duodenal portion of the common bile duct and of the sphincter. *Johns Hopkins Hosp. Bull.*, 1898, ix, 221–232; *Anat. Anz.*, 1900, xvii, 197–216.

Hermann, L. Neue Untersuchungen über Hautströme. *Arch. f. d. ges. Physiol.*, 1882, xxvii, 280–288.

Herring, P. T. and Simpson, S. The pressure of bile secretion and the mechanism of bile absorption in obstruction of the bile duct. *Proc. Roy. Soc. Med.*, Lond., 1907, lxxix B, 517–532.

Herschell, G. Gastric trouble of urinary origin. *Med. Press & Circ.*, 1905, cxxx, 559–560.

Hess, J. Versuche über die peristaltische Bewegung und über die Wirkung der Abführmittel. *Deutsches Arch. f. klin. Med.*, 1886, xl, 93–116.

Hesse, O. Zur Kenntnis des Brechaktes nach Röntgenversuchen an Hunden. *Arch. f. d. ges. Physiol.*, 1913, clii, 1–22.

Hicks, C. J., Jr. and Visher, J. W. Contributions to the physiology of the stomach. xxvii. The mechanism of regurgitation of duodenal contents into the stomach. *Am. J. Physiol.*, 1915, xxxix, 1–8.

Higgins, G. M. and Mann, F. C. Observations on the emptying of the gall-bladder. *Am. J. Physiol.*, 1926, lxxviii, 339–348.

Higgins, W. H. Clinical significance of hunger pains. Analysis of one hundred and sixty-two cases of gastro-intestinal and gall-bladder diseases. *J. Am. M. Assn.*, 1924, lxxxii, 599–601.

Hippocrates, The works of. Adams' Translation, New York, 1849, ii, 252.

Hirsch, A. (a) Untersuchungen über den Einfluss von Alkali und Saüre auf die motorischen Funktionen des Hundemagens. *Zentralbl. f. klin. Med.*, 1893, xiv, 73–77.

Hirsch, A. (b) Weitere Beiträge zur motorischen Funktion des Magens nach Versuchen an Hunden mit Darmfisteln. *Zentralbl. f. klin. Med.*, 1893, xiv, 377–383.

Hirsch, E. F. The gastric mucosa in delirium tremens. *Arch. Int. Med.*, 1916, xvii, 354–362.

Hoffmann, L. and Nather, K. Zur Anatomie der Magenarterien. Ein Beitrag zur Aetiologie des chronischen Magengeschwüres und seiner chirurgischen Behandlung. *Arch. f. klin. Chir.*, 1921, cxv, 650–671.

Hofmeister, F. and Schütz, E. Über die automatischen Bewegungen des Magens. *Arch. f. exper. Path. u. Pharmakol.*, 1885, xx, 1–33.

Hohlweg, H. Über Störungen der Salz-Säureabscheidung des Magens bei Erkrankungen und nach Exstirpation der Gallenblase. *Deutsches Arch. f. klin. Med.*, 1912, cviii, 255–276.

Holzknecht, G. Die normale Peristaltik des Kolon. *München. med. Wchnschr.*, 1909, lvi, 2401–2403.

Homans, J. Relation of pain in gastric and duodenal ulcer to muscular activity of the stomach. *Am. J. M. Sc.*, 1919, clvii, 74–83.

Hooker, D. ii. The effect of reversal of a portion of the spinal cord at the stage of the closed neural folds on the healing of the cord wounds, on the polarity of the elements of the cord and on the behavior of frog embryos. *J. Comp. Neurol.*, 1917, xxvii, 421–449.

Hotz, G. Beiträge zur Pathologie der Darmbewegungen. *Mitt. a. d. Grenzgeb. d. Med. u. Chir.*, 1909, xx, 257–318.

Houckgeest, Van Braam. Untersuchungen über Peristaltik des Magens und Darmkanals. *Arch. f. d. ges. Physiol.*, 1872, vi, 266–302.

Howard, R. L. and Sollmann, T. (a) The metabolic gradient of non-rhythmic strips from different levels of the turtle heart. *Am. J. Physiol.*, 1926, lxxix, 119–125.

Howard, R. L. and Sollmann, T. (b) The regional gradient of the turtle heart: isotonic sucrose solution on tone, rhythm and contractility. *Am. J. Physiol.*, 1926, lxxix, 126–129.

HRYNTSCHAK, T. Beiträge zur Physiologie des Ureters: I. Zur Harnleiterautomatie. *Arch. f. d. ges. Physiol.*, 1925, ccix, 542–561.

HUME, H. V., DENIS, W., SILVERMAN, D. N. and IRWIN, E. L. Hydrogen ion concentration in the human duodenum. *J. Biol. Chem.*, 1924, lx, 633–645.

HUNTER, G. W., JR. Notes on the heart action of Molgula Manhattensis (Verrill). *Am. J. Physiol.*, 1903, x, 1–27.

HUNTINGTON, G. S. The Anatomy of the Human Peritoneum and Abdominal Cavity. Philadelphia, 1903.

HURD-KARRER, A. M. A concentration gradient in corn stalks. *J. General Physiol.*, 1926, ix, 341–343.

HURST, A. F. The passage of food along the human alimentary canal. *Guy's Hosp. Rep.*, 1907, lxi, 389–427.

HURST, A. F. The study of constipation by means of the *x*-rays. *Arch. Roentg. Ray*, 1908, xiii, 3–10.

HURST, A. F. Constipation and Allied Disorders. London, 1909.

HURST, A. F. Diagnosis and treatment of duodenal ulcer. *Proc. Roy. Soc. Med.*, 1910, iii, 100–107.

HURST, A. F. The Sensibility of the Alimentary Canal. London, 1911.

HURST, A. F. Common fallacies in the *x*-ray diagnosis of disorders of the alimentary canal. *Arch. Roentg. Ray.*, 1912, xvii, 216–219.

HURST, A. F. (a) The cause and treatment of certain unfavorable after-effects of gastroenterostomy. *Ann. Surg.*, 1913, lviii, 466–472.

HURST, A. F. (b) The ileo-caecal sphincter. *J. Physiol.*, 1913, xlvii, 54–56.

HURST, A. F. The sphincters of the alimentary canal and their clinical significance. *Brit. M. J.*, 1925, i, 145–151.

HURST, A. F. and BRIGGS, P. J. The diagnosis of gastric and duodenal ulcer with the *x*-rays. *Guy's Hosp. Rep.*, 1924, lxxiv, 278–307.

HURST, A. F., COOK, F. and SCHLESINGER, E. G. The sensibility of the stomach and intestines in man. *J. Physiol.*, 1908, xxxvii, 481–490.

HURST, A. F. and NEWTON, A. The normal movements of the colon in man. *J. Physiol.*, 1913, xlvii, 57–65.

HUTCHISON, R. Conditions which simulate dyspepsia. *Brit. M. J.*, 1910, i, 485–488.

HYMAN, L. H. (a) On the action of certain substances on oxygen consumption. Action of potassium cyanide on planaria. *Am. J. Physiol.*, 1919, xlviii, 340–371.

HYMAN, L. H. (b) Physiological studies on planaria. I. Oxygen consumption in relation to feeding and starvation. *Am. J. Physiol.*, 1919, xlix, 377–402.

HYMAN, L. H. (c) Physiological studies on planaria. II. Oxygen consumption in relation to regeneration. *Am. J. Physiol.*, 1919, l, 67–81.

HYMAN, L. H. (d) Physiological studies on planaria. III. Oxygen consumption in relation to age (size) differences. *Biol. Bull.*, 1919, xxxvii, 388–403.

INAOKA, T. Studien über die Innervation und Peristaltik des Oesophagus beim Säuger. *Arch. f. d. ges. Physiol.*, 1924, cciii, 319–335.

INGVAR, S. Reaction of cells to the galvanic current in tissue cultures. *Proc. Soc. Exper. Biol. & Med.*, 1920, xvii, 198.

Ivanoff, W. Über die Regurgitation des Duodenuminhaltes in den nüchternen Magen. *Arch. f. Verdauungskr.*, 1926, xxxviii, 223–246.

Ivy, A. C. Contributions to the physiology of the stomach. *Arch. Int. Med.*, 1920, xxv, 6–31.

Ivy, A. C. Contributions to the physiology of the stomach. ix. The causes of gastric secretion: their practical significance and the mechanisms concerned. *J. Am. M. Assn.*, 1925, lxxxv, 877–880.

Ivy, A. C. (a) The newer physiology of the gastrointestinal tract. *Proc. Interstate Post-Graduate Medical Assembly of North America.* 1926, 199–204.

Ivy, A. C. (b) The relation of the gastrointestinal tract to pernicious anemia. *Northwest Med.*, 1926, xxv, 399–404.

Ivy, A. C. and Farrell, J. I. Contributions to the physiology of gastric secretion. viii. The proof of a humoral mechanism. A new procedure for the study of gastric physiology. *Am. J. Physiol.*, 1925, lxxiv, 639–649.

Ivy, A. C. and McIlvain, G. B. The excitation of gastric secretion by application of substances to the duodenal and jejunal mucosa. *Am. J. Physiol.*, 1923, lxvii, 124–140.

Ivy, A. C. and Oyama, Y. Studies on the secretion of the pars pylorica gastri. *Am. J. Physiol.*, 1921, lvii, 51–60.

Ivy, A. C., Vloedman, D. A. and Keane, J. The small intestine in hunger. *Am. J. Physiol.*, 1925, lxxii, 99–108.

Jacobj, C. Pharmakologische Untersuchung über das Colchicumgifte. *Arch. f. exper. Path. u. Pharmakol.*, 1890, xxvii, 119–157.

Jacobj, C. Beiträge zur physiologischen und pharmakologischen Kenntniss der Darmbewegungen mit besonderer Berücksichtigung der Beziehung der Nebenniere zu denselben. *Arch. f. Exper. Path. u. Pharmakol.*, 1891, xxix, 171–211.

Jaros, S. Über den Einfluss der Körperbewegung auf die motorischen Leistungen des Magens bei Eiweiss- und Kohlehydratfütterung. *Arch. f. d. ges. Physiol.*, 1917, clxviii, 112–123.

Jarotzky, A. Der Schliessungreflex des Pylorus als eine Funktionsprüfungsmethode des Pankreas und der Leber. *Zentralbl. f. d. Gesamtgeb. d. Med.*, 1927, xlviii, 11–14.

Jatrou, S. Über die arterielle Versorgung des Magens und ihre Beziehung zum Ulcus ventriculi. *Deutsche Ztschr. f. Chir.*, 1920, clix, 196–223.

Jefferson, G. The human stomach and the canalis gastricus. *J. Anat. & Physiol.*, 1915, xlix, 165–181.

Jenkins, O. P. and Carlson, A. J. The rate of nervous impulse in certain molluscs. *Am. J. Physiol.*, 1903, viii, 251–268.

Jennings, H. S. Modifiability in behavior. i. Behavior of sea anemones. *J. Exper. Zoöl.*, 1905, ii, 447–472.

Johnson, S. E. On the question of commissural neurones in the sympathetic ganglia. *J. Comp. Neurol.*, 1918, xxix, 385–404.

Johnson, S. E. Experimental observations on the nerve supply of the small intestine. *Anat. Record.*, 1923, xxv, 135–136.

Johnson, S. E. Experimental degeneration of the extrinsic nerves of the small intestine in relation to the structure of the myenteric plexus. *J. Comp. Neurol.*, 1925, xxxviii, 299–314.

Johnson, W. O. The function of the gall-bladder with special relation to the Meltzer-Lyon test. *Internat. Abstr. Surg.*, 1922, xxxiv, 177–182.

Jolasse. Zur Motilitätsprüfung des Magens durch Roentgenstrahlen. *Fortschr. a. d. Geb. d. Roentgenstrahlen*, 1907, xi, 47–53.

Jonas, S. Uber das Verhältniss zwischen Stuhlbild und Darmmotilität und die wechselnden Stuhlbilder der Hyperacidität und der Achylie. *Arch. f. Verdauungskr.*, 1912, xviii, 769–784.

Jones, C. M. The rational use of duodenal drainage. *Arch. Int. Med.*, 1924, xxxiv, 60–78.

Jones, N. W. Ileocecal incompetence. A clinical analysis of 1000 cases with some deductions therefrom. *Am. J. M. Sc.*, 1923, clxvi, 710–730.

Jonnesco, T. Structure de l'intestin grêle. Poirier et Charpy, Traité d'Anatomie Humaine, Ed. 2, Paris, 1901, p. 284.

Jordan, H. Die Physiologie der Locomotion bei Aplysia Limacina. *Ztschr. f. Biol.*, 1901, xli, 196–238.

Jordan, H. Uber reflexarme Tiere. *Ztschr. f. allg. Physiol.*, 1908, vii, 86–135.

Jordan, H. Vergleichende Physiologie wirbelloser Tiere. Jena, 1913.

Joseph, D. R. and Meltzer, S. J. Inhibition of the duodenum coincident with movements of the pyloric part of the stomach. *Am. J. Physiol.*, 1910, xxvii, xxxi–xxxii.

Judd, E. S. and Mann, F. C. The effect of removal of the gall-bladder. *Surg., Gynec. & Obst.*, 1917, xxiv, 437–442.

Judd, E. S. and Nagel, G. W. Duodenitis. *Ann. Surg.*, 1927, lxxxv, 380–390.

Jurica, E. J. Motility of denervated mammalian esophagus. *Am. J. Physiol.*, 1926, lxxvii, 371–384.

Kader, B. Ein experimenteller Beitrag zur Frage des localen Meteorismus bei Darmocclusion. *Ztschr. f. Chir.*, 1892, xxxiii, 57–124; 214–272.

Kahn, G. and Stokes, J. The comparison of the electrometric and colorimetric methods for determination of the pH of gastric contents. *J. Biol. Chem.*, 1926, lxix, 75–84.

Kahn, R. H. Studien über den Schluckreflex. Die sensible Innervation. *Arch. f. Physiol.*, 1903, Suppl. Bd., 386–426.

Kahn, R. H. (a) Studien über den Schluckreflex. ii. Die motorische Innervation der Speiseröhre. *Arch. f. Physiol.*, 1906, 355–361.

Kahn, R. H. (b) Studien über den Schluckreflex. iii. Zur Physiologie der Speiseröhre. *Arch. f. Physiol.*, 1906, 362–374.

Kantor, J. A study of atmospheric air in the upper digestive tract *Am. J. M. Sc.*, 1918, clv, 829–857.

Kaplan, S. F. Zur Lehre über den Einfluss der chirurgischen Veränderungen des Magens auf die Verdauungsprozesse. *Ztschr. f. Physiol. Chem.*, 1913, lxxxvii, 337–350.

Kast, L. Rückläufige Strömung in der Speiseröhre als Erklärung der belegten Zunge. *Berl. klin. Wchnschr.*, 1906, xliii, 947–950.

KAST, L. and MELTZER, S. J. Die Sensibilität der Bauchorgane. *Mitt. a. d. Grenzgeb. d. Med. u. Chir.*, 1909, xix, 586–616.

KÄSTLE, C. Ein Beitrag zur Kenntnis der Duodenalperistaltik und des Massentransportes im Duodenum. *Fortschr. a. d. Geb. d. Roentgenstrahlen*, 1923, xxx, 578–588.

KÄSTLE, C. and BRUEGEL, C. Die Bewegungsvorgänge des menschlichen Dünn- und Dickdarmes während der Verdauung auf Grund röntgenographischer und röntgenkinematographischer Untersuchungen. *München. med. Wchnschr.*, 1912, lix, 446–448.

KÄSTLE, C., RIEDER, H. and ROSENTHAL, J. Über kinematographisch aufgenommene Röntgenogramme der inneren Organe des Menschen. *München. med. Wchnschr.*, 1909, lvi, 280–282. Also separate monograph.

KATO, K. Ueber Gasresorption im Darm. *Internat. Beitr. z. Path. u. Therap. d. Ernährungsstör.*, 1910, i, 315–324.

KATSCH, G. Beitrag zum Studium der Magenmotilität. *Internat. Beitr. z. Path. u. Therap. d. Ernährungsstör.*, 1912, iii, 429–454.

KATSCH, G. Beiträge zum Studium der Darmbewegungen. III. Mitteilung. Pharmakologische Einflüsse auf den Darm bei physiologischer Versuchsanordnung. *Ztschr. f. exper. Path. u. Therap.*, 1913, xii, 253–289.

KATSCH, G. and BORCHERS, E. (a) Beiträge zum Studium der Darmbewegungen. I. Mitteilung. Das Experimentelle Bauchfenster. *Ztschr. f. exper. Path. u. Therap.*, 1913, xii, 225–236.

KATSCH, G. and BORCHERS, E. (b) Über physikalische Beeinflussung der Darmbewegungen. *Ztschr. f. exper. Path. u. Therap.* 1913, xii, 237–252.

KATSCH, G. and FRIEDRICH, L. Ueber die funktionelle Bedeutung der Magenstrasse. *Mitt. a. d. Grenzgeb. d. Med. u. Chir.*, 1921, xxxiv, 343–361.

KATSCHKOVSKI. Das Ueberleben der Hunde nach einer gleichzeitigen doppelten Vagotomie am Halse. *Arch. f. d. ges. Physiol.*, 1901, lxxxiv, 6–56.

KAUFMANN, R. Anatomisch-experimentelle Studien über die Magenmuskulatur. *Ztschr. f. Heilk.*, 1907, xxviii; Abt. f. Path. Anat., 203–238.

KEETON, R. W. Nausea and related sensations elicited by duodenal stimulation. *Arch. Int. Med.*, 1925, xxxv, 687–697.

KEITH, A. Anatomical evidence as to the nature of the caecum and appendix. *J. Anat. & Physiol.*, 1903, xxxviii, vii–xx.

KEITH, A. (a) An account of six specimens of the great bowel removed by operation; with some observations on the motor mechanism of the colon. *Brit. J. Surg.*, 1915, ii, 576–599.

KEITH, A. (b) The Cavendish Lecture on a new theory of the causation of enterostasis. *Lancet*, 1915, ii, 371–375.

KEITH, A. and JONES, F. W. A note on the development of the fundus of the human stomach. *J. Anat. & Physiol.*, 1902, xxxvi, 34–38.

KELLING, G. Studien zur Chirurgie des Magens. *Arch. f. klin. Chir.*, 1900, lxii, 1–42, 288–338.

KELLING, G. Ueber den Mechanismus der acuten Magendilatation. *Arch. f. klin. Chir.*, 1901, lxiv, 393–417.

KELLING, G. Untersuchungen über die Spannungszustände der Bauchwand, der Magen- und der Darmwand. *Ztschr. f. Biol.*, 1903, xliv, 161–258.

KIENBÖCK, R. Zur Röntgendiagnose der Colitis ulcerosa. *Fortschr. a. d. Geb. d. Röntgenstrahlen*, 1913, xx, 231–239.

KING, C. E. Studies on intestinal inhibitory reflexes. *Am. J. Physiol.*, 1924, lxx, 183–193.

KING, C. E. and ARNOLD, L. The activities of the intestinal mucosal motor mechanism. *Am. J. Physiol.*, 1922, lix, 97–121.

KING, C. E., ARNOLD, L. and CHURCH, J. G. The physiological rôle of the intestinal mucosal movements. *Am. J. Physiol.*, 1922, lxi, 80–92.

KIRSCHNER, M. and MANGOLD, E. Die motorische Funktion des Sphincter pylori und des Antrum pylori beim Hunde nach der queren Durchtrennung des Magens. *Mitt. a. d. Grenzgeb. d. Med. u. Chir.*, 1911, xxiii, 446–494.

KIRSTEIN, A. Experimentelles zur Pathologie des Ileus. *Deutsche med. Wchnschr.*, 1889, xv, 1000–1002.

KLEE, P. Der Einfluss der Splanchnikusreizung auf den Ablauf der Verdauungsbewegungen. Röntgenversuche an der Katze. *Arch. f. d. ges. Physiol.*, 1913, cliv, 552–570.

KLEE, P. and KLÜPFEL, O. Experimentelle Beitrag zur Funktion der Gallenblase. *Mitt. a. d. Grenzgeb. d. Med. u. Chir.*, 1914, xxvii, 785–795.

KLEIN, E. Gastric motility. I. The origin and character of gastric peristalsis. *Arch. Surg.*, 1926, xii, 571–582; II. The conduction of the gastric peristaltic wave. *Ibid.*, pp. 583–590; III. The mechanism of the pylorus. *Ibid.*, pp. 1224–1254.

KNOWLTON, F. P. and MOORE, A. R. Note on the reversal of reciprocal inhibition in the earthworm. *Am. J. Physiol.*, 1917, xliv, 490–491.

KOENNECKE, W. Experimentelle Innervationstörungen am Magen und Darm. *Ztschr. f. d. ges. exper. Med.*, 1922, xxviii, 384–412.

KOENNECKE, W. and MEYER, H. Röntgenuntersuchungen über den Einfluss von Vagus und Sympathicus auf Magen und Darm. *Mitt. a. d. Grenzgeb. d. Med. u. Chir.*, 1922, xxxv, 297–323.

KÖLBING, P. Beiträge zur Magendarmchirurgie. *Beitr. z. klin. Chir.*, 1902, xxxiii, 518–534.

KÖLLIKER, A. Handbuch der Gewebelehre des Menschen. Ed. 6, Leipzig, 1902, Band 3.

KRAUS, F. (a) Die Bewegungen der Speiseröhre unter normalen und pathologischen Verhältnissen auf Grund röntgen-kinematographischen Untersuchungen. *Ztschr. f. exper. Path. u. Therap.*, 1912, x, 363–380.

KRAUS, F. (b) Ueber die Bewegungen der Speiseröhre unter normalen und pathologischen Verhältnissen (auf Grund röntgen-kinematographischer Untersuchungen). *Deutsche. med. Wchnschr.*, 1912, xxxviii, 393–395.

KREHL, R. Über die Folgen der Vagusdurchschneidung. *Arch. f. Physiol.*, 1892, suppl. Bd., 278–290.

KREIDL, A. and MÜLLER, A. Beiträge zur Physiologie des Verdauungstraktes: Mitt. I, II, III. *Arch. f. d. ges. Physiol.*, 1907, cxvi, 159–185.

KRETSCHMER, H. L. The retrograde movement of ureteral calculi. *J. Am. M. Assn.*, 1918, lxxi, 1355–1359.

KROGH, A. The number and distribution of capillaries in muscles, with calculations of the oxygen pressure head necessary for supplying the tissue. *J. Physiol.*, 1919, lii, 409–415.

KRZYWANEK, F. W. Vergleichende Untersuchungen über die Mechanik der Verdauung. I. Mitteilung. Einleitung. Untersuchungen am Hund. *Arch. f. d. ges. Physiol.*, 1927, ccxv, 481–518.

KUNTZ, A. The distribution of sympathetic neurones in the myenteric and submucous plexuses in the small intestine of the cat. *Anat. Record.*, 1918, xiv, 42.

KÜPFERLE, L. Zur Physiologie des Schluckmechanismus nach röntgenkinomatographischen Aufnahmen. *Arch. f. d. ges. Physiol.*, 1913, clii, 579–588.

KURODA, M. Observations of the effects of drugs on the ileo-colic sphincter. *J. Pharmacol. & Exper. Therap.*, 1916, ix, 187–195.

KUSSMAUL, A. Die peristaltische Unruhe des Magens, nebst Bemerkungen über Tiefstand und Erweiterung desselben, das Klatschgeräusch und Galle im Magen. *Samml. klin. Vortr.* (Volkmann), 1880, 1637–1674.

LAIGNEL-LAVASTINE. Recherches sur le Plexus Solaire. Paris Thèse, 1903.

LAKE, N. C. Observations upon the growth of tissues in vitro relating to the origin of the heart-beat. *J. Physiol.*, 1916, l, 364–369.

LANGENDORFF, O. Die Beziehungen der Nervenfasern des Halssympathicus zu den Ganglienzellen des oberen Halsknotens. *Zentralbl. f. Physiol.*, 1891, v, 129–131.

LANGLEY, J. N. The arrangement of the sympathetic nervous system, based chiefly on observations upon pilo-motor nerves. *J. Physiol.*, 1893, xv, 176–244.

LANGLEY, J. N. On the question of commissural fibers between nerve cells having the same function and situated in the same sympathetic ganglion, and on the function of post-ganglionic nerve plexuses. *J. Physiol.*, 1904, xxxi, 244–259.

LANGLEY, J. N. Trophic centre of the afferent fibres accompanying the sympathetic nerves. *J. Physiol.*, 1905, xxxiii, 17–18.

LANGLEY, J. N. and ANDERSON, H. K. The constituents of the hypogastric nerves. *J. Physiol.*, 1894–95, xvii, 177–191.

LANGLEY, J. N. and ANDERSON, H. K. On the innervation of the pelvic and adjoining viscera. Part I. The lower portion of the intestine. *J. Physiol.*, 1895, xviii, 67–105.

LANGLEY, J. N. and ANDERSON, H. K. (a) The innervation of the pelvic and adjoining viscera. Part VI. Histological and physiological observations upon the effects of section of the sacral nerves. *J. Physiol.*, 1896, xix, 372–384.

LANGLEY, J. N. and ANDERSON, H. K. (b) The innervation of the pelvic and adjoining viscera. Part VII. Anatomical observations. *J. Physiol.*, 1896, xx, 372–406.

LANGLEY, J. N. and MAGNUS, R. Some observations of the movements of the intestine before and after degenerative section of the mesenteric nerves. *J. Physiol.*, 1905, xxxiii, 34–51.

Langmann, G. A. On Antiperistaltic Movement. New York, 1900, p. 375.

Lansdown, R. G. P. and Williamson, G. S. The etiology of appendicitis, gastric ulcer, and allied conditions. *Brit. J. Surg.*, 1914, ii, 306–324.

Lapicque, M. et Mme. L. Durée des processus d'excitation pour différents muscles. *Compt. rend. Acad. d. sc.*, 1905, cxl, 801–804.

Laqueur, E. Die verschiedene Geschwindigkeit der Darmbewegungen bei verschiedenen Tieren. *Zentralbl. f. Physiol.*, 1914, xxvii, 274–275.

Larimore, J. W. The human large intestine in the new-born and in the adult. *Ann. Clin. Med.*, 1926, v, 439–463.

Latarjet, A., Bonnet, P. and Bonniot, A. Les nerfs du foie et des voies biliaires. *Lyon Chirurg.*, 1920, xvii, 13–35.

Latarjet, A. and Forgeot, E. Circulation artérielle de l'intestin grêle. *J. de l'anat. et physiol.*, 1910, xlvi, 483–510.

Lebon, H. and Aubourg, P. Contractions reflexes du gros intestin par excitation de l'estomac. *Presse méd.*, 1913, xxi, 566–567.

Ledderhose. Ein Fall von Gastroenterostomie wegen Stenose des unteren Duodenum. *Arch. f. klin. Chir.*, 1899, lix, 153–156.

Lee, F. S., Guenther, A. E. and Meleny, H. E. Some of the general physiological properties of diaphragm muscle as compared with certain other mammalian muscles. *Am. J. Physiol.*, 1916, xl, 446–473.

Leggett, N. B. and Maury, J. W. Draper. Studies upon the function of the pylorus and stoma after gastro-enterostomy has been performed. *Ann. Surg.*, 1907, xlvi, 549–555.

Legros and Onimus. Recherches experimentales sur les mouvements de l'intestin. *J. de l'anat. et. physiol.*, 1869, 37–66.

Lehman, E. P. and Gibson, H. V. Observations in a case of jejunal fistula. *J. Am. M. Assn.*, 1924, lxxxii, 1918–1920.

Lehmann, A. v. Studien über reflektorische Darmbewegungen beim Hunde. *Arch. f. d. ges. Physiol.*, 1913, cxlix, 413–433.

Lehmann, W. Die Beziehungen zwischen Magen und Darm mit besonderer Berücksichtigung der nach Magenoperationen auftretenden Darmstörungen. *Arch. f. klin. Chir.*, 1923, cxxiii, 433–501.

Lehmann, W. Über das Erbrechen. *Klin. (-therap.) Wchnschr.*, 1924, iii, 1937–1939.

Lenk, R. and Eisler, F. Experimentell-radiologische Studien zur Physiologie und Pathologie des Verdauungstraktes. *München. med. Wchnschr.*, 1913, lx, 1031–1032.

Lenz, E. Ueber die normalen Darmbewegungen und die Peristaltik-wirkung der Anthrachinonabführmittel nach Beobachtungen am Dickdarm-Bauchfenster der Katze., *Schweiz. Wchnschr. f. Chem. u. Pharm.*, 1923, liii, 887–893, 912–916, 935–938.

Lesné, E., Binet, L. and Paulin, A. La Traversée Digestive Chez le Nourrisson Variations Biologiques et Pathologiques. *Arch. de Med. d'Enf.*, 1920, xxiii, 449–456.

Leven, M. G. Radioscopie gastrique appliquée à l'étude du séjour des liquides dans l'estomac. *Compt. rend. Soc. de biol.*, 1902, liv, 1478–1480.

Levy-Dorn and Mühlfelder, S. Über den Brechakt im Röntgenbilde. *Berl. klin. Wchnschr.*, 1910, xlvii, 388.

Lewis, D. and Grulee, C. G. The pylorus after gastro-enterostomy for congenital pyloric stenosis. A report on its condition two hundred and fifty-six days following the operation. *J. Am. M. Assn.*, 1915, lxiv, 410–412.

Lewis, F. T. The form of the stomach in human embryos with notes upon the nomenclature of the stomach. *Am. J. Anat.*, 1912, xiii, 477–503.

Lewis, M. R. Rhythmical contraction of the skeletal muscle tissue observed in tissue cultures. *Am. J. Physiol.*, 1915, xxxviii, 153–161.

Lewis, M. R. Spontaneous rhythmical contraction of the muscles of the bronchial tubes and air sacs of the chick embryo. *Am. J. Physiol.*, 1924, lxviii, 385–388.

Lewis, M. R. and Lewis, W. H. The contraction of smooth muscle cells in tissue cultures. *Am. J. Physiol.*, 1917, xliv, 67–74.

Lewis, T. The Mechanism and Graphic Registration of the Heart Beat. New York, 1920.

Lewis, T. and Mathison, G. C. Auriculo-ventricular heart-block as a result of asphyxia. *Heart*, 1910, ii, 47–53.

Lichty, M. J. Influence of perigastric lesions on gastric secretion. *J. Am. M. Assn.*, 1910, lv, 1799–1803.

Lieb, C. C. and McWhorter, J. E. Action of drugs on the isolated gall-bladder. *J. Pharmacol. Exper. Therap.*, 1915, vii, 83–98.

Lieb, C. W. The effects of an exclusive long-continued meat diet based on the history, experiences and clinical survey of Vilhjalmur Stefansson, Arctic Explorer. *J. Am. M. Assn.*, 1926, lxxxvii, 25–26.

Lillie, R. S. The conditions determining the rate of conduction in irritable tissues and especially in nerves. *Am. J. Physiol.*, 1914, xxxiv, 414–445.

Lillie, R. S. The formation of structures resembling organic growths by means of electrolytic local action in metals and the general physiological significance and control of this type of action. *Biol. Bull.*, 1917, xxxiii, 135–186.

Lillie, R. S. The nature of protoplasmic and nervous transmission. *J. Phys. Chem.*, 1920, xxiv, 165–191.

Link, R. Untersuchungen über die Entleerung des Magens bei verschiedenen Lagen des Körpers. *Deutsches Arch. f. klin. Med.*, 1901, lxxi, 175–188.

Lintvareff, S. I. Über die Rolle der Fette beim Übergang des Mageninhalts in den Darm. *Biochem. Centralbl.*, 1903, i, 96–97.

Litten, M. Über die Folgen des Verschlusses der Arteria mesaraica superior. *Virchow's Arch. f. path. Anat.*, 1875, lxiii, 289–321.

Loeb, J. Comparative Physiology of the Brain and Comparative Psychology. New York, 1900.

Loeb, J. The Dynamics of Living Matter. New York, 1906.

London, E. S. Zur Kenntnis des Verdauungs- und Resorptionsgesetze. 1. Mitt: Methodische Angaben. *Ztschr. f. physiol. Chem.*, 1910, lxv, 189–192.

London, E. S. Experimentelle Physiologie und Pathologie der Verdauung (Chymologie). Berlin, 1925.

London, E. S. and Dobrowolskaja, N. A. xxxi Mitt. Weitere Untersuchungen über die Verdauungs- resp. Resorptionsgesetze. *Ztschr. f. physiol. Chem.*, 1909, lx, 270–273.

London, E. S. and Sandberg, F. Zum Chemismus der Verdauung im tierischen Körper. xx. Mitt. Zur Kenntniss der Verdauungs- und Resorptionsgezetze im Magendarmkanal. *Ztsch. f. physiol. Chem.*, 1908, lvi, 394–403.

London, E. S. and Sivre, A. Zum Chemismus der Verdauung und Resorption im tierischen Körper. *Ztschr. f. physiol. Chem.*, 1909, lx, 194–266.

Long, J. H. and Fenger, F. On the normal reaction of the intestinal tract. *J. Am. Chem. Soc.*, 1917, xxxix, 1278–1286.

Löwenthal, M. Beiträge zur Diagnostik und Therapie der Magenkrankheiten. *Berl. klin. Wchnschr.*, 1892, xxix, 1188–1190.

Lucas, D. R. Studies of the peristalsis of the ureter of dogs by the graphic method. *Am. J. Physiol.*, 1906, xvii, 392–407.

Luciani, L. Human Physiology. London, 1913, ii, 232–236.

Luckhardt, A. B., Phillips, H. T. and Carlson, A. J. Contributions to the physiology of the stomach. li. The control of the pylorus. *Am. J. Physiol.*, 1919, l, 57–66.

Lüderitz, C. Experimentelle Untersuchungen über die Entstehung der Darmperistaltik. *Virchow's Arch. f. path. Anat.*, 1889, cxviii, 19–36.

Lüderitz, C. Experimentelle Untersuchungen über die Entstehung der Darmperistaltik. *Virchow's Arch. f. path. Anat.*, 1890, cxxii, 1–28.

Lüderitz, C. Das motorische Verhalten des Magens bei Reizung seiner ausseren Fläche. *Arch. f. d. ges. Physiol.*, 1891, xlix, 158–174.

Lüdin, M. Der Einfluss von Zwischenmahlzeiten bei der röntgenologischen Prüfung der Magenmotilität. *Deutsche med. Wchnschr.*, 1913, xxxix, 1239–1241.

Lund, E. J. Control of morphological polarity by means of the electric current. Proc. Amer. Soc. Zool. *Anat. Record*, 1921, xx, 188.

Lund, E. J. Experimental control of organic polarity by the electric current. iv. The quantitative relations between current density, orientation, and inhibition of regeneration. *J. Exper. Zool.*, 1924, xxxix, 357–379.

Luschka, H. Die organische Musculatur innerhalb verschiedener Falten des menschlichen Bauchfelles, *Arch. f. Anat. u. Physiol.*, 1862, 202–209.

Lyman, H. The receptive relaxation of the colon. *Am. J. Physiol.*, 1913, xxxii, 61–64.

Lyon, B. B. V. Diagnosis and treatment of diseases of the gallbladder and biliary ducts. Preliminary report on a new method. *J. Am. M. Assn.*, 1919, lxxiii, 980–982.

Lyon, B. B. V. (a) The treatment of catarrhal jaundice by a rational, direct and effective method. *Am. J. M. Sc.*, 1920, clix, 503–512.

Lyon, B. B. V. (b) Can the gall-bladder, biliary ducts and liver be medically drained? *Am. J. M. Sc.*, 1920, clx, 515–544.

Macalister, A. Contributions to the comparative anatomy and physiology of the gall-bladder. *Med. Press and Circ.*, 1867, iv, 129–131; 150–153.

Macarthur, C. G. and Jones, O. C. Some factors influencing the respiration of ground nervous tissue. *J. Biol. Chem.*, 1917, xxxii, 259–274.

Macewen, W. The function of the caecum and appendix. *Lancet*, 1904, ii, 995–1000.

MacFadyen, A., Nencki, M. and Sieber, N. Research into the chemical processes in the small intestine of man. *J. Anat. & Physiol.*, 1891, xxv, 390–427.

Mackenzie, W. C. The spleen in monotremes and marsupials. *J. Anat.*, 1916, li, 1–18.

Mackenzie, W. C. Further studies on the peritoneum and intestinal tract in monotremes and marsupials. *J. Anat. & Physiol.*, 1917, li, 278–292.

Magnus, R. (a) i. Mitteil: Versuche am überlebenden Dünndarm von Säugethieren. *Arch. f. d. ges. Physiol.*, 1904, cii, 123–151.

Magnus, R. (b) ii. Mitteil: Die Beziehungen des Darmnervensystems zur automatischen Darmbewegung. *Arch. f. d. ges. Physiol.*, 1904, cii, 349–363.

Magnus, R. (c) iii. Mitteil: Die Erregungsleitung. *Arch. f. d. ges. Physiol.*, 1904, ciii, 515–524.

Magnus, R. (d) iv. Mitteil: Rhythmizität und refraktäre Periode. *Arch. f. d. ges. Physiol.*, 1904, ciii, 525–540.

Magnus, R. (e) v. Mitteil: Wirkungsweise und Angriffspunkt einiger Gifte am Katzendarm. *Arch. f. d. ges Physiol.*, 1905, cviii, 1–71.

Magnus, R. (f) vi. Mitteil: Versuche am überlebenden Dünndarm von Säugetieren. *Arch. f. d. ges. Physiol.*, 1906, cxi, 152–160.

Magnus, R. Die Bewegungen des Verdauungskanals. *Ergebn. d. Physiol.*, 1908, vii, 27–64.

Magnus, R. Die Bewegungen des Verdauungsrohres. Tigerstedt's Handbuch der physiologischen Methodik. Leipzig, 1911, xi, Abth. 2, 99–149.

Magnus, R. Bemerkungen zur vorstehenden Entgegnung von Professor A. Valenti. *Arch. f. d. ges. Physiol.*, 1914, clvii, 75–78.

Magnus, R. Die physiologische und therapeutische Bedeutung des Cholins für die Magen- Darmtätigkeit. *München. m. Wchnschr.*, 1925, lxxii, 249–251.

Maleyx, H. Contribution a l'étude des hemorrhagies et des perforations intestinales à distance au cours des obstructions terminales du gros intestin. Paris, *Thèse*, 1912.

Mall, F. P. Die motorischen Nerven der Portalvene. *Arch. f. Physiol.*, 1890, Suppl. 57–58.

Mall, F. P. Der Einfluss des Systems der Vena portae auf die Verteilung des Blutes. *Arch. f. Physiol.*, 1892, 409–453.

Mall, F. P. (a) The vessels and walls of the dog's stomach. *Johns Hopkins Hosp. Rep.*, 1896, i, 1–36.

Mall, F. P. (b) A study of the intestinal contractions. *Johns Hopkins Hosp. Rep.*, 1896, i, 37–75.

Mall, F. P. (c) Reversal of the intestine. *Johns Hopkins Hosp. Rep.*, 1896, i, 93–110.

Mann, F. C. A comparative study of the anatomy of the sphincter at the duodenal end of the common bile duct with special reference to species of animals without a gall-bladder. *Anat. Rec.*, 1920, xviii, 355–360.

Mann, F. C. The production by chemical means of a specific cholecystitis. *Ann. Surg.*, 1921, lxxiii, 54–57.

Mann, F. C. The functions of the gall-bladder. *Physiol. Rev.*, 1924, iv, 251–273.

Mann, F. C. and Bollman, J. L. The relation of the gall-bladder to the development of jaundice following obstruction of the common bile duct. *J. Lab. & Clin. Med.*, 1925, x, 540–543.

Mann, F. C., Bollmann, J. L. and Magath, T. B. Studies on the physiology of the liver: ix. The formation of bile pigment after total removal of the liver. *Am. J. Physiol.*, 1924, lxix, 393–409.

Mann, F. C., Brimhall, S. D. and Foster, J. P. (a) The extrahepatic biliary tract in common domestic and laboratory animals. *Anat. Rec.*, 1920, xviii, 47–66.

Mann, F. C., Brimhall, S. D. and Foster, J. P. (b) The relation of the common bile duct to the pancreatic duct in common domestic and laboratory animals. *J. Lab. and Clin. Med.*, 1920, v, 203–206.

Mann, F. C. and Foster, J. P. The secretory pressure of the liver with special reference to the presence or absence of a gall-bladder. *Am. J. Physiol.*, 1918, xlvii, 278–282.

Mann, F. C. and Kawamura, K. Duodenectomy, an experimental study. *Ann. Surg.*, 1922, lxxv, 208–220.

Mann, F. C. and Williamson, C. S. The experimental production of peptic ulcer. *Ann. Surg.*, 1923, lxxvii, 409–422.

Marbaix, O. Le passage pylorique. *Cellule*, 1898, xiv, 249–332.

Martin, C. L. and Rogers, F. T. Hunger pain. *Am. J. Roentgenol.*, 1927, xvii, 222–227.

Mathews, A. P. Electrical polarity in the hydroids. *Am. J. Physiol.*, 1902, viii, 294–299.

Matsuno, Y. Über die Muskulatur des Ductus choledochus. *Virchow's Arch. f. path. Anat.*, 1923, ccxlvii, 208–215.

May, W. P. The innervation of the sphincters and musculature of the stomach. *J. Physiol.*, 1904, xxxi, 260–271.

Mayer, A. G. Nerve conduction, and other reactions in Cassiopea. *Am. J. Physiol.*, 1916, xxxix, 375–393.

Mayer, S. Erbrechen. Hermann's Handbuch der Physiologie, 1883, v, 444.

Mayo, W. J. The technic of gastrojejunostomy. *Ann. Surg.*, 1906, xliii, 537–542.

Mayo, W. J. Gastric ulcer. *J. Am. M. Assn.*, 1915, lxv, 1069–1073.

Mayo, W. J. Radical operations on the stomach with especial reference to mobilization of the lesser curvature. *Surg., Gynec. & Obst.*, 1923, xxxvi, 447–453.

Mayo, W. J. Discussion on anesthesia. *Proc. Staff Meetings of the Mayo Clinic*, 1926, i, 107.

McClendon, J. F. (a) New hydrogen electrodes and rapid methods of determining hydrogen ion concentrations. *Am. J. Physiol.*, 1915, xxxviii, 180–185.

McClendon, J. F. (b) Acidity curves in the stomachs and duodenums of adults and infants, plotted with the aid of improved methods of measuring the hydrogen ion concentration. *Am. J. Physiol.*, 1915, xxxviii, 191–199.

McClendon, J. F., Bissell, F. S., Lowe, E. R. and Meyer, P. F. Hydrogen ion concentration of the contents of the small intestine. *J. Am. M. Assn.*, 1920, lxxv, 1638–1641.

McClendon, J. F., Myers, F. J., Culligan, L. C. and Gydesen, C. S. Factors influencing the hydrogen ion concentration of the ileum. *J. Biol. Chem.*, 1919, xxxviii, 535–538.

McClendon, J. F., Shedlov, A. and Karpman, B. The hydrogen ion concentration of the contents of the small intestine. *J. Biol. Chem.*, 1918, xxxiv, 1–3.

McClure, C. W., Montague, O. C. and Campbell, L. L. (a) The pH and buffer values of duodenal contents derived from normal men. *Arch. Int. Med.*, 1924, xxxiii, 525–532.

McClure, C. W., Montague, O. C. and Campbell, L. L. (b) The chemical reaction of duodenal contents. *Bost. M. & Surg.*, J., 1924, cxc, 237–239.

McClure, C. W., Reynolds, L. and Schwartz, C. O. On the behavior of the pyloric sphincter in normal man. *Arch. Int. Med.*, 1920, xxvi, 410–423.

McClure, C. W., Wetmore, A. S. and Reynolds, L. New methods for estimating enzymatic activities of duodenal contents of normal man. *Arch. Int. Med.*, 1921, xxvii, 706–715.

McClure, R. D. and Derge, H. F. A study of reversal of the intestine. *Johns Hopkins Hosp. Bull.*, 1907, xviii, 472–474.

M'Crea, E. D. The abdominal distribution of the vagus. *J. Anat.*, 1924, lix, 18–40.

M'Crea, E. D. and M'Swiney, B. A. The effect of stimulation of the vagi on the pyloric region of the stomach. *J. Physiol.*, 1926, lxi, 28–34.

M'Crea, E. D., M'Swiney, B. A., Morison, J. W. and Stopford, J. B. The normal movements of the stomach. *Quart. J. Exper. Physiol.*, 1924, xiv, 379–397.

M'Crea, E. D., M'Swiney, B. A. and Stopford, J. S. B. Effects of section of the vagi nerves on the motor activity of the stomach. *J. Physiol.*, 1925, lx, Proc., xxix.

M'Crea, E. D., M'Swiney, B. A. and Stopford, J. S. B. The effect on the stomach of section of the vagi nerves. *Quart. J. Exper. Physiol.*, 1926, xvi, 195–203.

McGill, C. The structure of smooth muscle in the resting and in the contracted condition. *Am. J. Anat.*, 1909, ix, 493–545.

McGuigan, H. and Becht, F. C. The site of the action of strychnine. *J. Pharmacol. & Exper. Therap.*, 1914, v, 469–478.

McGuigan, H., Keeton, R. W. and Sloan, L. H. The segmental action of strychnine. *J. Pharmacol & Exper. Therap.*, 1916, viii, 143–154.

McIver, M. A., Benedict, E. B. and Cline, J. W. Postoperative gaseous distention of the intestine. *Arch. Surg.*, 1926, xiii, 588–604.

McIver, M. A., Redfield, A. C. and Benedict, E. B. Gaseous exchange between the blood and the lumen of the stomach and intestines. *Am. J. Physiol.*, 1926, lxxvi, 92–111.

McMaster, P. D. and Elman, R. On the expulsion of bile by the gall-bladder and a reciprocal relationship with the sphincter activity. *J. Exper. Med.*, 1926, xliv, 173–198.

McWhorter, G. L. Some clinical and experimental observations on gastric acidity. Use of the gas chain method. *Am. J. M. Sc.*, 1918, clv, 672–685.

McWhorter, G. L. The surgical significance of the common bile duct sphincter. *Surg., Gynec. & Obst.*, 1921, xxxii, 124–130.

Meek, W. J. The regeneration of nerve and muscle in the small intestine. *Am. J. Physiol.*, 1910, xxv, 367–384.

Mellinger, C. Beiträge zur Kenntniss des Erbrechens. *Arch. f. d. ges. Physiol.*, 1881, xxiv, 232–245.

Meltzer, S. J. Direct and indirect faradization of the digestive canal. *N. York M. J.*, 1895, lxi, 746–750.

Meltzer, S. J. On the causes of the orderly progress of the peristaltic movements in the esophagus. *Am. J. Physiol.*, 1899, ii, 266–272.

Meltzer, S. J. (a) Secondary peristalsis of the esophagus—a demonstration on a dog with a permanent fistula. *Proc. Soc. Exper. Biol. & Med.*, 1907, iv, 35–37.

Meltzer, S. J. (b) Deglutition through an esophagus partly deprived of its muscularis, with demonstration. *Proc. Soc. Exper. Biol. & Med.*, 1907, iv, 40–42.

Meltzer, S. J. The disturbance of the law of contrary innervation as a pathogenetic factor in the diseases of the bile ducts and the gall-bladder. *Am. J. M. Sc.*, 1917, cliii, 469–477.

Meltzer, S. J. and Auer, J. Vagus reflexes upon esophagus and cardia. *Brit. M. J.*, 1906, ii, 1806–1807.

Meltzer, S. J. and Auer, J. Peristaltic rush. *Am. J. Physiol.*, 1907, xx, 259–281.

Mentzer, S. H. The valves of Heister. *Arch. Surg.*, 1926, xiii, 511–522.

Mering, J. von. Über die Function des Magens. *Verhandl. d. deutsch. Kong. f. innere Med.*, 1893, xii, 471–487.

Mering, J. von. Zur Funktion des Magens. *Verhandl. d. Kong. f. inn. Med.*, 1897, xv, 433–440.

Merkel, F. Handbuch der Topographischen Anatomie. Braunschweig, 1899, ii, 570–578.

Merzbacher, L. Die Folgen der Durchschneidung der sensibeln Wurzeln im unteren Lumbalmarke, im Sacralmarke und in der Cauda equina des Hundes. *Arch. f. d. ges. Physiol.*, 1902, xcii, 585–604.

Meyer, E. Ist die Entleerung des Magens abhängig von dem Grad der Säurebildung? *Arch. f. Verdauungkr.*, 1903, ix, 537–541.

Meyer, K. F., Neilson, N. M. and Feusier, M. T. The mechanism of gall-bladder infection in laboratory animals. *J. Infect. Dis.*, 1921, xxviii, 456–509.

Mikulicz, J. von. Beiträge zur Physiologie der Speiseröhre und der Cardia. *Mitt. a. d. Grenzgeb. d. Med. u. Chir.*, 1903, xii, 569–601.

Milani, E. La funzionalità del tenue (digiuno) studiata con la seriografia. *Radiol. med.*, 1923, x, 409–415.

Miller, F. R. On gastric sensation. *J. Physiol.*, 1910, xl, 409–415.

Mines, G. R. On the spontaneous movements of amphibian skeletal muscle in saline solutions, etc. *J. Physiol.*, 1908, xxxvii, 408–444.

Mines, S. R. Note on the survival of an excised muscle under aseptic conditions. *J. Physiol.*, 1910, xl, Proc., xvii–xviii.

Mitchell, P. C. On the intestinal tract of mammals. *Tr. Zoöl. Soc.*, London, 1905, xvii, 437–536.

Mitchell, W. T. and Stifel, R. E. The pressure of bile secretion during chronic obstruction of the common bile duct. *Johns Hopkins Hosp. Bull.*, 1916, xxvii, 78–79.

Monks, G. H. Intestinal localization. *Tr. Am. Surg. Ass.*, 1903, xxi, 405–424.

Monks, G. H. Studies in the surgical anatomy of the small intestine and its mesentery. *Ann. Surg.*, 1905, xlii, 543–569.

Moody, R. O., Van Nuys, R. S. and Chamberlain, W. E. Position of the stomach, liver, and colon. Results of a roentgenologic study in six hundred healthy adults. *J. Am. M. Assn.*, 1923, lxxxi, 1924–1931.

Moore, A. R. Reversal of reaction by means of strychnine in planarians and starfish. *J. General Physiol.*, 1918, i, 97–100.

Moore, A. R. On the nature of inhibition in Pennatula. *Am. J. Physiol.*, 1926, lxxvi, 112–115.

Morat. Sur l'innervation motrice de l'estomac. *Lyon med.*, 1882, xl, 289–296; 335–341.

Morat. Sur quelques particularités de l'innervation motrice de l'estomac et de l'intestin. *Arch. de physiol. norm. et path.*, 1893, v, 142–153.

Morishima, K. and Fujitani, J. Zur Untersuchungsmethode der spontanen Bewegung des Froschmagens. *Arch. f. exper. Path.*, Suppl. B, 1908, 407–414.

Moritz. (a) Ueber die Functionen des Magens. *München. med. Wchnschr.*, 1895, xlii, 1143–1147.

Moritz. (b) Studien über die motorische Thätigkeit des Magens. i. Mitteilung. Ueber das Verhalten des Druckes im Magen. *Ztschr. f. Biol.*, 1895, xxxii 313–369.

Moritz. Studien über die motorische Thätigkeit des Magens. ii. Mitteilung: Über die Beeinflussung der Geschwindigkeit der Magenentleerung durch die Beschaffenheit der Ingesta. *Ztschr. f. Biol.*, 1901, xlii, 565–611.

Morse, W. E. The relation of acid to gastric discharge and duodenal regurgitation in the dog. *Am. J. Physiol.*, 1916, xli, 439–448.

Morse, W. E. The effect of various neutral solutions on gastric discharge, gastric secretion, and duodenal regurgitation. *Arch. Int. Med.*, 1918, xxi, 48–58.

Moszkowicz, L. Zur Histologie des ulkusbereiten Magens. *Arch. f. klin. Chir.*, 1922, cxxii, 444–499.

Moynihan, B. G. A. A case of gastro-jejunostomy for complete rupture of the intestine at the duodenojejunal flexure. *Brit. M. J.*, 1901, i, 1136.

Moynihan, B. G. A. Abdominal Operations. Philadelphia. 1906.

Mühsam, R. Experimentelles zur Frage der Antiperistaltik. *Mitt. a. d. Grenzgeb. d. Med. u. Chir.*, 1900, vi, 451–461.

Muirhead, A. L. and Gerald, H. F. The action of certain volatile oils on isolated intestinal segments. *J. Pharmacol. & Exper. Therap.*, 1916, viii, 253–260.

Müller, A. Beiträge zur Kenntnis von Schutzeinrichtungen des Darmtraktes gegen spitze Fremdkörper. *Arch. f. d. ges. Physiol.*, 1904, cii, 206–216.

Müller, A. and Hesky, O. Über die Folgeerscheinungen nach operativer Entfernung der Darmmuskulatur, insbesondere am Dickdarm und Rectum. *Mitt. a. d. Grenzgeb. d. Med. u. Chir.*, 1911, xxii, 104–110.

Müller, A. and Kondo, K. Über die Folgeerscheinungen nach operativer Entfernung der Längsmuskulatur des Darmes. *Mitt. a. d. Grenzgeb. d. Med. u. Chir.*, 1912, xxiv, 512–515.

Müller, E. Beiträge zur Kenntnis des autonomen Nervensystems. i. Ueber die Entwicklung des Sympathicus und des Vagus bei den Selachiern. *Arch. f. mikr. Anat.*, 1920, xliv, 208–247.

Müller, L. R. Beiträge zur Anatomie, Histologie und Physiologie des Nervus vagus, zugleich ein Beitrag zur Neurologie des Herzens, der Bronchien, und des Magens. *Deutsches Arch. f. klin. Med.*, 1911, ci, 421–481.

Müller, L. R. Die Darminnervation. *Deutsches Arch. f. klin. Med.*, 1912, cv, 1–43.

Müller, L. R. Über den Durst und über die Durstempfindung. *Deutsche med. Wchnschr.*, 1920, xlvi, 113–116.

Müller-Hettlingen, J. Über galvanische Erscheinungen an keimenden Samen. *Arch. f. d. ges. Physiol.*, 1883, xxxi, 193–214.

Murphy, F. T. and Brooks, B. Intestinal obstruction, an experimental study of the causes of symptoms and death. *Arch. Int. Med.*, 1915, xv, 392–412.

Murray, H. A. Jr. (a) Physiological ontogeny. A. Chicken embryos. x. The temperature characteristic for the contraction rate of isolated fragments of embryonic heart muscle. *J. General Physiol.*, 1926, ix, 781–788.

Murray, H. A. Jr. (b) Physiological ontogeny. A. Chicken embryos. The pH, chloride, carbonic acid, and protein concentrations in the tissues as functions of age. *J. General Physiol.*, 1926, ix, 789–803.

Murray, H. A. Jr. (c) Physiological ontogeny. A. Chicken embryos. xii. The metabolism as a function of age. *J. General Physiol.*, 1926, x, 337–344.

Myers, F. J. and McClendon, J. F. Note on the hydrogen ion concentration of the human duodenum. *J. Biol. Chem.*, 1920, xli, 187–190.

Nakanishi, M. The innervation of the pyloric sphincter in the rat. *J. Physiol.*, 1924, lviii, 480–484.

Neilson, C. H. and Lipsitz, S. T. The effect of various procedures on the passage of liquids from the stomach. *J. Am. M. Assn.*, 1915, lxiv, 1052–1055.

Neuburger, M. History of Medicine. Translated by Playfair. London, 1910, i, 29.

Neumann, K. O. The afferent fibers of the abdominal vagus in the rabbit and cat. *J. Physiol.*, 1914, xlix, 34–37.

Nice, L. B. and Neill, Alma J. Types of oscillations in diaphragm muscle. *Am. J. Physiol.*, 1921, lvii, 171–178.

Niwa, S. The effect of cocaine hydrochloride on the CO_2 production of the mixed nerve fiber. *J. Pharmacol. & Exper. Therap.*, 1919, xii, 323–342.

Northrop, J. H. The kinetics of the decomposition of peroxide by catalase. *J. General Physiol.*, 1925, vii, 377–387.

Nothnagel, C. W. H. Beiträge zur Physiologie und Pathologie des Darmes. Berlin, 1884.

Oddi, R. D'une disposition à sphincter spéciale de l'ouverture du canal cholédoque. *Arch. ital. de biol.*, 1887, viii, 317–322.

Oddi, R. Effetti dell estirpazione della cystifellea. *Bull. d. sc. med.*, Bologna. 1888, xxi, 194–202. Abstracted in *Centralbl. f. Chir.*, 1889, xvi, 140.

Oddi, R. Di una speciale disposizione di sfintere allo sbocco del coledoco. *Ann. d. Univ. libera di Perugia, Facult. di med. e chir.*, 1887, ii, 249–264. Also (*Quoted from Luciani*) *Monitor zool. ital.*, 1894, v, 216.

Oddi, R. Sulla fisio-patologia delle vie biliari. *Confer. clin. ital.*, Milano, 1897–1898, i, 77–97.

Ogata, M. Ueber die Verdauung nach der Ausschaltung des Magens. *Arch. f. Physiol.*, 1883, 89–116.

Ogata, S. The activity of the isolated uterus. *J. Pharmacol. & Exper. Therap.*, 1921, xviii, 185–200.

Okada, A. On the contractile movement of the gall-bladder. *J. Physiol.*, 1916, l, 42–46.

Okada, S. and Arai, M. The hydrogen-ion concentration of the intestinal contents. *J. Biol. Chem.*, 1922, li, 135–139.

Openchowski, T. (a) Über die gesammte Innervation des Magens. *Deutsche med. Wchnschr.*, 1889, xv, 717–719.

Openchowski, T. (b) Über die nervösen Vorrichtungen des Magens. *Zentralbl. f. Physiol.*, 1889, iii, 1–10.

Oppel, A. Lehrbuch der vergleichenden mikroskopischen Anatomie der Wirbeltiere. Erster Teil-Der Magen. Jena, 1896, Zweite Teil. Schlund und Darm, 1897.

Oppenheimer, Z. Ueber die motorischen Vorrichtungen des Magens. *Deutsche med. Wchnschr.*, 1889, xv, 125–128.

Ortmayer, M. Gastric motor activity in patients with peptic ulcer. *Arch. Int. Med.*, 1925, xxxv, 423–432.

Ortner, A. Ein Beitrag zur Kenntniss der Magenentleerung und ihrer Beziehung zur Verdünnungssekretion des Magens. *Arch. f. d. ges. Physiol.*, 1917, clxviii, 124–134.

Oser, L. Experimentelle Beiträge zur Innervation des Magens. i. Zur Innervation des Pylorus. ii. Zur Innervation des Magens. *Ztschr. f. klin. Med.*, 1892, xx, 285–297.

Ostwald, W. Periodische Erscheinungen bei der Auflösung des Chroms in Säuren. *Ztschr. f. Physikal Chemie*, 1900, xxxv, 33–76, 204–256.

Otto, E. Über das Verhalten von Salzlösungen im Magen. *Arch. f. exper. Path. u. Pharmakol.*, 1905, lii, 370–388.

Pal, J. Ueber Beziehungen zwischen Splanchnicus und Rectum. *Wien. klin. Wchnschr.*, 1896, ix, 204.

Palmer, W. L. (a) The mechanism of pain in gastric and duodenal ulcers. i. Achlorhydria. *Arch. Int. Med.*, 1926, xxxviii, 603–611.

Palmer, W. L. (b) The mechanism of pain in gastric and duodenal ulcers. ii. The production of pain by means of chemical irritants. *Arch. Int. Med.*, 1926, xxxviii, 694–707.

Palmer, W. L. The mechanism of pain in gastric and in duodenal ulcer. iii. The rôle of peristalsis and spasm. *Arch. Int. Med.*, 1927, xxxix, 109–133.

Palugyay, J. Röntgenologische Beobachtungen über die Anatomie und Physiologie der Kardia. *Arch. f. d. ges. Physiol.*, 1921, clxxxvii, 232–242.

Palugyay, J. Die Diagnose des beginnenden Kardia-Karzinoms mittels Durchleuchtung in Beckenhochlagerung und über die Röntgenologie der Kardia überhaupt. *Fortschr. a. d. Geb. d. Röntgenstrahlen*, 1922, Kongresshefte, xiii, 35–38.

Palugyay, J. Röntgenstudien über den oesophagealen Schluckakt. Ein Beitrag zur Speiseröhrenphysiologie. *Arch. f. d. ges. Physiol.*, 1923, cc, 620–641.

Parker, G. H. (a) The rate of transmission in the nerve net of the coelenterates. *J. Gen. Physiol.*, 1918, i, 231–236.

Parker, G. H. (b) Some underlying principles in the structure of the nervous system. *Science*, 1918, xlvii, 151–162.

Parker, G. H. The Elementary Nervous System. Philadelphia, 1919.

Parnas, T. Energetick glatter Muskeln. *Arch. f. d. ges. Physiol.*, 1910, cxxxiv, 441–495.

Paterson, H. J. Appendicular gastralgia or the appendix as a cause of gastric symptoms. *Proc. Roy. Soc. Med.*, 1910, iii, 187–208.

Paukul, E. Die Zuckungsformen von Kaninchenmuskeln verschiedener Farbe und Structur. *Arch. f. Anat. u. Entwcklngsgesch*, 1904, Physiol. Abth., 100–120.

Pavloff, I. P. Die physiologische Chirurgie des Verdauungskanals. *Ergebn. d. Physiol.*, 1902, i, 246–284.

Pavloff, .I P. The Work of the Digestive Glands. Translated by Thompson, W., London, 1910, Ed. 2.

Pavloff, I. P. Die operative Methodik des Studiums der Verdauungsdrüsen. Tigerstedt's Handbuch der physiologischen Methodik. Leipzig, 1911, ii, zw. Abth., 150–188.

Payne, W. W. and Poulton, E. P. Visceral pain in the upper alimentary tract. *Quart. J. Med.*, 1923, xvii, 53–80.

Pearce, R. G. A history of the physiology of digestion. *Cleveland M. J.*, 1914, xiii, 343–350.

Pearcy, J. F. and Van Liere, E. J. Reflexes from the colon. Reflexes to the stomach. *Am. J. Physiol.*, 1926, lxxviii, 64–73.

Penfield, W. G. Contraction waves in the normal and hydronephrotic ureter; an experimental study. *Am. J. M. Sc.*, 1920, clx, 36–46.

Penzoldt, F. Beiträge zur Lehre von der menschlichen Magenverdauung unter normalen und abnormen Verhältnissen. i. Untersuchungsmethode. ii. Verdaulichkeit der Nahrung. iii. Das chemische Verhalten des Mageninhalts während der normalen Verdauung. *Deutsches Arch. f. klin. Med.*, 1893, li, 535–582; 1894, liii, 209–234.

Pepper, O. H. P. The influence on gastric secretion of aseptic foreign bodies in the gall-bladder. *Am. J. M. Sc.*, 1913, cxlvi, 220–222.

PERMAN, E. Der Nervenapparat des Magens und das Geschwür der kleinen Kurvatur. *Arkiv. f. Kirurgi.* See *Nord. med. Ark.*, 1919, li, 355–382.

PEYER, A. Über Magenaffektionen bei männlichen Genitalleiden. *Samml. klin. Vortr.* (Volkmann), 1890, iv, 3169–3204.

PFUNGEN, R. VON and ULLMAN. Über die Bewegungen des Antrum pylori beim Menschen. *Zentralbl. f. Physiol.*, 1887, i, 275–279.

PLANT, O. H. and MILLER, G. H. The effects of carminative volatile oils. *J. Pharmacol. and Exper. Therap.*, 1926, xxvii, 149–164.

POENSGEN, E. Die motorischen Verrichtungen des menschlichen Magens und ihre Störungen mit Ausschluss der Lehre vom Erbrechen. Strassburg, 1882.

POHL, J. Über Darmbewegungen und ihre Beeinflussung durch Gifte. *Arch. f. exper. Path. u. Pharmakol.*, 1894, xxxiv, 87–104.

POIRIER and CHARPY. Traité d'Anatomie Humaine. Paris, 1901, Ed. 2, iii, 771.

POKORNY, LILLY. Röntgenologische Untersuchungen über die Wirkung von Tierkohle bei Meteorismus. *Fortschr. a. d. Geb. d. Röntgenstrahlen*, 1923, xxxi, 192–201.

POMPILIAN. Sur la contraction musculaire de l'Escargot. *Compt. rend. Soc. de. biol.*, 1899, li, 489–490.

PORTER, E. L. Variations in irritability of the reflex arc. II. Variations under strychnine. *Am. J. Physiol.*, 1915, xxxvi, 171–182.

PORTIS, S. A. and PORTIS, B. Effects of subtotal gastrectomy on gastric secretion. Experimental studies by aid of a Pavloff pouch in dogs. *J. Am. M. Assn.*, 1926, lxxxvi, 836–839.

POTTER, J. C. and MANN, F. C. Pressure changes in the biliary tract. *Am. J. M. Sc.*, 1926, clxxi, 202–217.

POULTON, E. P. An investigation of the cause and relief of pain in gastric ulcer. *Lancet*, 1921, i, 263–265.

PREISS, G. A. Ausschaltung der Bauchhöhlensensibilität durch Blockierung der Nervi splanchnici und der Rami communicantes des lumbalen Grenzstranges. *Deutsche Ztschr. f. Chir.*, 1920, clix, 59–101.

PRESSLER, K. Beobachtungen und Versuche über den normalen und inversen Situs viscerum et cordis bei Anurenlarven. *Arch. f. Entwcklngsmechn. d. Organ.*, 1911, xxxii, 1–35.

PRUTZ, W. and ELLINGER, A. Über die Folgen der Darmgegenschaltung. Zugleich ein Beitrag zur Lehre von der Indicanurie. *Arch. f. klin. Chir.*, 1902, lxvii, 964–995.

PRUTZ, W. and ELLINGER, A. Über die Folgen der Darmgegenschaltung. II. Mitteil: Zugleich ein Beitrag zur Frage der sogenannten Antiperistaltik. *Arch. f. klin. Chir.*, 1904, lxxii, 415–448.

PUHL, H. Über die Bedeutung entzündlicher Prozesse für die Entstehung des Ulcus ventriculi et duodeni. *Virchow's Arch. f. path. Anat.*, 1926, cclx, 1–109.

QUIMBY, A. J. Roentgen interpretation of intestinal conditions. *Am. J. Roentgenol.*, 1914, i, 399–403.

QUIROT, M. La forme Gastrique de l'Occlusion Intestinale Chronique. Paris, *Thése*, 1909.

Raasche, A. Über eigentümliche Veränderungen der Herztätigkeit unter dem Einfluss von Chloroform. *Ztschr. f. Biol.*, 1911, lv, 469–490.

Rammstedt, C. Die Operation der angeborenen Pylorusstenose. *Zentrbl. f. Chir.*, 1913, xl, 3–4; also *Med. Klin*, 1912, viii, 1702–1705.

Ranson, S. W. Afferent paths for visceral reflexes. *Physiol. Rev.*, 1921, i, 477–479.

Ranvier, L. A. Leçons d'Anatomie Generale Faites au College de France. Paris, 1880, 433.

Rasdolsky, I. Reflexe und sensible Phänomene von seiten des Nervus vagus bei chirurgischen Erkrankungen der inneren Organe. *Beitr. z. klin. Chir.*, 1924, cxxxii, 200–214.

Reach, F. Über rückläufige Fortbewegung von Darminhalt. *Prag. med. Wchnschr.*, 1902, xxvii, 549–550.

Reach, F. Der Schliessmuskel des Ductus choledochus in funktioneller Beziehung. *Arch. f. exper. Path. u. Pharmacol.*, 1920, lxxxv, 178–198.

Redwitz, E. F. von. Die Physiologie des Magens nach Resektion aus der Kontinuität. *Mitt. a. d. Grenzgeb. d. Med. u. Chir.*, 1917, xxix, 531–620.

Reeves, T. B. A study of the arteries supplying the stomach and duodenum and their relation to ulcer. *Coll. Papers Mayo Clinic*, 1919, xi, 3–22; *Surg., Gynec. & Obst.*, 1920, xxx, 374–385.

Rehfuss, M. E., Bergeim, O. and Hawk, P. B. Gastro-intestinal studies. 1. The question of the residuum found in the empty stomach. *J. Am. M. Assn.*, 1914, lxiii, 11–13.

Reichel, P. Zur Pathologie des Ileus und Pseudoileus. *Deutsche Ztschr. f. Chir.*, 1893, xxxv, 495–553.

Reichmann, M. Über sogenannte Dyspepsia acida. *Berl. klin. Wchnschr.*, 1884, xxi, 768–771.

Reis, V. van der and Schembra, F. W. Länge und Lage des Verdauungsrohres beim Lebenden. *Ztschr. f. d. ges. exp. Med.*, 1924, xliii, 94–115.

Reis, V. van der and Schembra, F. W. Ist die Magenstrasse beim Menschen als Gleitbahn der Ingesta anzusehen? *Arch. f. Verdauungskr.*, 1926, xxxix, 76–89.

Reynolds, L. and McClure, C. W. Mótor phenomena occurring in normal stomachs, in the presence of peptic ulcer and its pain, as observed fluoroscopically. *Arch. Int. Med.*, 1922, xxix, 1–11.

Richter, C. P. Action currents from the stomach. *Am. J. Physiol.*, 1924, lxvii, 612–633.

Rieder, H. Die physiologische Dünndarm-Bewegung beim Menschen. *Fortschr. a. d. Geb. d. Röntgenstrahlen*, 1925, xxxiii, 461–468.

Robertson, H. E. and Hargis, E. H. Duodenal ulcer; an anatomic study. *Med. Clin. N. Am.*, 1925, viii, 1065–1092.

Robertson, T. B. Studies in comparative physiology, 1. Observations on the physiology of the fly's intestine. *Trans. Roy. Soc. S. Australia*, 1920, xliv, 97–109.

Rogatz, J. L. Roentgen-ray studies of stomach function. *Am. J. Dis. Child.*, 1924, xxviii, 53–68.

ROGERS, F. T. and HARDT, L. L. J. Contributions to the physiology of the stomach. XXVI. The relation between the digestive contractions of the filled, and the hunger contractions of the "empty" stomach. *Am. J. Physiol.*, 1915, xxxviii, 274–284.

ROITH, O. Die physiologische Bedeutung der einzelnen Dickdarmabschnitte, zugleich ein Beitrag zur Lehre von der Antiperistaltik. *Mitt. a. d. Grenzgeb. d. Med. u. Chir.*, 1909, xix, 33–52.

ROITH, O. Über die Peristaltik und Antiperistaltik des menschlichen Dickdarmes. *Mitt. a. d. Grenzgeb. d. Med. u. Chir.*, 1913, xxv, 203–210.

ROLLESTON, H. D. and JEX-BLAKE, A. J. On the occurrence of vomiting during rectal alimentation. *Brit. M. J.*, 1903, ii, 68–69.

ROMANES, G. J. Preliminary observations on the locomotor system of medusae. *Philosph. Tran. Roy. Soc. England*, 1876, clxvi, 269–313.

ROSENBERG, S. Die physiologischen Folgen der Gastroenterostomie. *Arch. f. d. ges. Physiol.*, 1898, lxxiii, 403–421.

ROSSBACH, M. J. (a) Beiträge zur Lehre von den Bewegungen des Magens, Pylorus und Duodenums. *Deutsches Arch. f. klin. Med.*, 1890, xlvi, 296-322.

ROSSBACH, M. J. (b) Beobachtungen über die Darmbewegung des Menschen. *Deutsches Arch. f. klin. Med.*, 1890, xlvi, 323-328.

ROST, F. Die anatomischen Grundlagen der Dickdarmperistaltik. *Arch. f. klin. Chir.*, 1912, xcviii, 984–992.

ROST, F. Die funktionelle Bedeutung der Gallenblase. Experimentelle und anatomische Untersuchungen nach Cholecystektomie. *Mitt. a. d. Grenzgeb. d. Med. u. Chir.*, 1913, xxvi, 710–770.

ROST, F. The Pathological Physiology of Surgical Diseases. Translated by Reimann, S. P., Phila., 1923.

ROUS, P. and MCMASTER, P. D. The concentrating activities of the gall-bladder. *Proc. Soc. exper. Biol. and Med.*, 1920, xvii, 215–216.

ROUS, P. and MCMASTER, P. D. The concentrating activity of the gall-bladder. *J. Exper. Med.*, 1921, xxxiv, 47–73.

ROUX, J. C. and BALTHAZARD, V. (a) Sur l'emploi des rayons de Röntgen pour l'étude de la motricité stomacale. *Compt. rend. Soc. de biol.*, 1897, xlix, 567–569.

ROUX, J. C. and BALTHAZARD, V. (b) Note sur les fonctions motrices de l'estomac du chien. *Compt. rend. Soc. de biol.*, 1897, xlix, 704–706.

ROUX, J. C. and BALTHAZARD V. (c) Étude des contractions de l'estomac chez l'homme à l'aide des rayons de Röntgen. *Compt. rend. Soc. de biol.*, 1897, xlix, 785–787.

ROUX, J. C. and BALTHAZARD, V. Étude du fonctionnement moteur de l'estomac à l'aide des rayons de Röntgen. *Arch. de Physiol.*, 1898, x, 85–94.

RUBASCHOFF, S. Beitrag zur Lehre über die Folgen der Vagotomie. *Internat. Beitr. z. Path. u. Therap. d. Ernährungsstör.*, 1912, iii, 462–484.

RUGE, E. Beiträge zur Kentniss der Darmgase. *Chem. Zentralbl.*, 1862, vii, 347–364.

RUTHERFORD, A. H. The Ileocecal Valve. New York, 1914.

Sabbatani, L. Nuovo metodo per osservare le intestina. *Arch. di fisiol.*, 1909, vi, 265–268.

Sanders, H., Ezn. Methode tot onderzoek der peristaltische Bewegingen van het darmkanaal, enz. Voorloop. mededeel. Abstract in *Centralbl. f. d. med., Wissensch.*, 1871, 479.

Satani, Y. Experimental studies of the ureter. *Am. J. Physiol.*, 1919, xlix, 474–495.

Sauer, L. W. The non-surgical treatment of pyloric stenosis. *Am. J. Dis. Child.*, 1921, xxii, 166–180.

Schäfer, E. A. Text-book of Microscopic Anatomy. London, 1912, ii, 536–552.

Scheier, M. Zur Verwertung der Röntgenstrahlen für die Physiologie des Schluckaktes. *Fortschr. a. d. Geb. d. Rontgenstrahlen.*, 1912, xviii, 377–391.

Scheunert, A. Über die Schichtung des Mageninhaltes nebst Bemerkungen über ihre Bedeutung für die Stärkeverdauung. *Arch. f. d. ges. Physiol.*, 1917, clxix, 201–240.

Schiefferdecker, P. Untersuchung einer Anzahl von Kaumuskeln des Menschen und einiger Säugetiere in bezug auf ihren Bau und ihre Kernverhältnisse nebst einer Korrektur meiner Herzarbeit. *Arch. f. d. ges. Physiol.*, 1919, clxxiii, 265–384.

Schierbeck, N. P. Fernere Untersuchungen über das Auftreten der Kohlensäure im Magen. *Skand. Arch. f. Physiol.*, 1895, v, 1–12.

Schiff, E., Eliasberg, H. and Mosse, K. Zur Pathogenese der Ernährungsstörungen beim Säugling. iii. Mitteilung: Untersuchungen am Duodenalsaft. *Jahrb. f. Kinderh.*, 1923, cii, 277–290.

Schillbach, E. Studien über den Einfluss der Elektricität auf den Darm. *Virchow's Arch. f. path. Anat.*, 1887, cix, 278–288.

Schilling, F. Wasser im Munde, Wasserspeien, Wasserkolik. *Zentralbl. f. inn. Med.*, 1915, xxxvi, 501–516.

Schlippe, P. Physikalische Untersuchungen bei der Anwendung des Magenschlauches. *Deutsches Arch. f. klin. Med.*, 1903, lxxvi, 450–473.

Schloffer, H. Über Ileus bei Hysterie. *Beitr. z. klin. Chir.*, 1899, xxiv, 392–417.

Schmidt, J. E. Ein Beitrag zur Frage der Magensensibilität. *Mitt. a. d. Grenzgeb. d. Med. u. Chir.*, 1909, xix, 278–281.

Schoemaker, J. Über die motorische Funktion des Magens. *Mitt. a. d. Grenzgeb. d. Med. u. Chir.*, 1910, xxi, 719–728.

Schoen, R. (a) Experimentelle Untersuchungen über Meteorismus. i. Teil. Diffusion und Resorption der Darmgase unter physiologischen Bedingungen. *Deutsches Arch. f. klin. Med.*, 1925, cxlvii, 224–244.

Schoen, R. (b) Experimentelle Untersuchungen über Meteorismus. ii. Teil. Veränderungen der Gasresorption im Darm unter pathologischen Bedingungen, besonders des Kreislaufs und des Muskeltonus. *Deutsches Arch. f. klin. Med.*, 1925, cxlviii, 86–110.

Schreiber, J. Ueber den Schluckmechanismus. *Arch. f. exper. Path. u. Pharmakol.*, 1901, xlvi, 414–447.

Schreiber, J. (a) Über die normalen Vorgänge beim Schlucken und die Schluckkraft. *Arch. f. Verdauungskr.*, 1911, xvii, 647–676.

Schreiber, J. (b) Zur Lehre vom Schluckmechanismus. *Arch. f. exper. Pathol. u. Pharmakol.*, 1911, lxvii, 72–88.

Schreiber, J. Über den bewegenden Einfluss der Schwerkraft beim Trinken in aufrechter- und Kopfstellung. *Arch. f. Verdauungskr.*, 1915, xxi, 1–15.

Schüle, A. Untersuchungen über die Sekretion und Motilität des normalen Magens. *Ztschr. f. klin. Med.*, 1895, xxviii, 461–504; 1896, xxix, 49–90.

Schultz, P. Die glatte Musculatur der Wirbelthiere (mit Ausnahme der Fische). *Arch. f. Anat. u. Entwcklngsgesch.*, 1895, Physiol. Abth., p. 517–550.

Schultz, P. Zur Physiologie der längsgestreiften (glatten) Muskeln der Wirbelthiere. iv. Beitrag. *Arch. f. Anat. u. Entwcklngsgesch.*, 1903, Physiol. Abth., Suppl., 1–148.

Schüpbach, A. Über den Einfluss der Galle auf die Bewegung des Dünndarms. *Ztschr. f. Biol.*, 1908, li, 1–41.

Schür, H. Über Hyperaciditätschmerzen und Ulcus ventriculi. *Med. Klin.*, 1911, vii, 919–921.

Schütz, E. Über Hyperacidität. *Wien. med. Wchnschr.*, 1906, lvi, 2241–2249.

Schwartz, E. Über die Totalexstirpation des Magens. *Zentralbl. f. Chir.*, 1926, liii, 578–584.

Schwartzenberg, C. Die peristaltische Bewegung des Dünndarms. *Ztschr. f. rationelle Med.*, 1849, vii, 311–331.

Schwarz, G. Über hypokinetische und dyskinetische Formen der Obstipation. *München. med. Wchnschr.*, 1912, lix, 2153–2155.

Segale, G. C. Sulla funzione motoria dell'intestino. *Arch. ital. di Chir.*, 1921, iv, 101–164.

Segale, M. The temperature of acutely inflamed peripheral tissue. *J. Exper. M.*, 1919, xxix, 235–249.

Senn, N. Intestinal Surgery. Chicago, 1889.

Shaklee, A. O. and Anderson, F. O. Vomiting reflex from stomach after vagotomy. *Proc. Soc. Exper. Biol. and Med.*, 1924, xxi, 488.

Sherrington, C. S. The Integrative Action of the Nervous System. New Haven, 1911.

Sherrington, C. S. Postural activity of muscle and nerve. *Brain*, 1915, xxxviii, 191–234.

Shimodaira, Y. Experimentelle Untersuchungen über die Entstehung von sogenannten Dehnungsgeschwüren des Darmes. *Mitt. a. d. Grenzgeb. d. Med. u. Chir.*, 1911, xxii, 229–310.

Shipley, P. G. and Blackfan, K. D. The pharmacological action of adrenalin on the sphincter pylori of the foetus. *Johns Hopkins Hosp. Bull.*, 1922, xxxiii, 159–162.

Short, A. R. Observations on the ileo-cecal valve. *Brit. M. J.*, 1919, ii, 164–165.

Sick, K. and Tedesko, F. Studien uber Magenbewegung mit besonderer Berüchsichtigung der Ausdehnungsfähigkeit des Hauptmagens (Fundus). *Deutsches Archiv. f. klin. Med.*, 1908, xcii, 416–451.

Silverman, A. N. and Menville, L. J. Observations of the visualized gallbladder by the Graham method with reference to the effect of non-surgical

biliary drainage: preliminary report. *J. Am. M. Assn.*, 1925, lxxxiv, 416–418.

Singer, G. and Holzknecht, G. Über objektive Befunde bei der spastischen Obstipation. *München. med. Wchnschr.*, 1911, lviii, 2537–2539.

Sinnhuber. Beiträge zur Lehre vom muskulären Cardiaverschluss. *Ztschr. f. klin. Med.*, 1903, l, 102–119.

Sippy, B. W. Gastric and duodenal ulcer, medical cure by an efficient removal of gastric juice corrosion. *J. Am. M. Ass.*, 1915, lxiv, 1625–1630.

Slowtzoff, B. Appareil pour l'étude de l'activité de l'intestin en dehors de l'organisme. *Compt. rend. Soc. de biol.*, 1916, lxxix, 84–85.

Smith, C. H. and Lewald, L. T. The influence of posture on digestion in infancy. *Am. J. Dis. Child.*, 1915, ix, 261–282.

Smith, M. I. The action of the autonomic drugs on the surviving stomach. *Am. J. Physiol.*, 1918, xcvi, 232–243.

Sokoloff, O. and Luchsinger, B. Zur Physiologie der Ureteren. *Arch. f. d. ges. Physiol.*, 1881, xxvi, 464–469.

Soper, H. W. The story of magnesium sulfate with especial reference to its use in biliary drainage. *Am. J. M. Sc.*, 1925, clxix, 398–407.

Sosman, M. C., Whitaker, L. R. and Edson, P. J. Clinical and experimental cholecystography. *Am. J. Roentgenol.*, 1925, xiv, 495–503.

Soyesima, Y. Experimentelle und literarische Studien über die ausgedehnten Dünndarmresektionen. *Deutsche. Ztschr. f. Chir.*, 1911, cxii, 425–466.

Spadolini, I. Le azioni antagonistiche nei sistemi autonomi. *Arch. di fisiol.*, 1916, xv, 1–168.

Spadolini, I. Contributo allo studio dell' innervazione estrinseca dello stomaco e dell' intestino tenue. *Arch. di fisiol.*, 1917, xv, 229–243.

Spencer, W. H., Meyer, G. P., Rehfuss, M. E. and Hawk, P. B. Gastro-intestinal studies. xii. Direct evidence of duodenal regurgitation and its influence upon the chemistry and function of the normal human stomach. *Am. J. Physiol.*, 1916, xxxix, 459–479.

Stahnke. Magen- und Duodenalbeobachtung bei oesophagealer Vagusreizung. *Fortschr. a. d. Geb. d. Röntgenstrahlen*, 1925, xxxiii, 18–19.

Steele, J. D. The relation of excessive gastric acidity to gastric symptoms. *J. Am. M. Assn.*, 1906, xlvii, 496–500.

Steinberg, M. E. Stomach mucosa in ulcer and in carcinoma. Histologic studies. *Arch. Surg.*, 1927, xiv, 991–1022.

Stenhouse, H. M. Cholecystitis of chemical origin in man following inhalations of poison gas. *U. S. Nav. Med. Bull.*, 1923, xix, 291–296.

Stewart, G. D. and Barber, W. H. Segmental resection for gastric ulcer. *Ann. Surg.*, 1916, lxiv, 527–536.

Stierlin, Die radiologische Diagnostik der Ileo-coecaltuberkulose und anderer ulcerativer und indurierender Dickdarmprozesse. *Zentralbl. f. Röntgenstrahlen*, 1911, ii, 254.

Stierlin, E. and Fritzsche, E. Discussion on the colon of baboons. *Verhandl. d. Kong. f. innere Med.*, 1912, xxix, 183–188.

Stiles, P. G. On the rhythmic activity of the oesophagus and the influence upon it of various media. *Am. J. Physiol.*, 1901, v, 338–357.

Stookey, B. P. Bladder and rectal disturbances in spinal cord tumors. *Arch. Neurol. and Psychiat.*, 1923, x, 519–531.
Straub, W. Zur Muskelphysiologie des Regenwurms. *Arch. f. d. ges. Physiol.*, 1900, lxxix, 379–399.
Straub, W. Zur Physiologie des Aplysienherzens. *Arch. f. d. ges. Physiol.*, 1901, lxxxvi, 504–532.
Straub, W. Fortgesetzte Studien am Aplysienherzen (Dynamik, Kreislauf und dessen Innervation) nebst Bemerkungen zur vergleichenden Muskelphysiologie, *Arch. f. d. ges. Physiol.*, 1904, ciii, 429–449.
Strauss, A. A. Complete exclusion of the large bowel. *J. Am. M. Assn.*, 1916, lxvi, 267–271.
Strauss, A. A. Longitudinal resection of the lesser curvature, with resection of pyloric sphincter for gastric ulcer: an experimental and clinical study. *J. Am. M. Assn.*, 1924, lxxxii, 1765–1770.
Strauss, H. Über Magengährungen und deren diagnostiche Bedeutung. *Ztschr. f. klin. Med.*, 1894, xxvi, 514–535.
Strauss, H. Über die Entstehung von Schwefelwasserstoff und Indol im menschlichen Magen durch bacterielle Eiweisszersetzung. *Berl. klin. Wchnschr.*, 1896, xxxiii, 385–389.
Sudler, M. T. The architecture of the gall bladder. *Johns Hopkins Hosp. Bull.*, 1901, xii, 126–129.
Surmont, H. and Dubus, A. De l'excitation à distance de la motricité colique. *Arch. de mal. de l'appar. digest.*, 1912, vi, 181–195.
Suyling, J. P. Beitrag zur Kenntnis der Hyperesthesie für Salzsäure. *Berl. klin. Wchnschr.*, 1888, xxv, 869–870.
Sweet, J. E. The gall-bladder: its past, present, and future. *Internat. Clin.*, 1924, i, 187–226.
Swiezynski, J. Nachprüfung der Grütznerschen Versuche über das Schicksal von Rectalinjectionen an Menchen und Thieren. *Deutsche med. Wchnschr.*, 1895, xxi, 514–516.
Symes, W. L. Observations on anaesthesia by phenylethylmalonyl urea. *J. Physiol.*, 1915, xlix, 126–132.

Tabora, von. Über motorische Magenreflexe. *Zentralbl. f. Röntgenstrahlen*, 1912, ii, 247.
Takahashi, M. Die Abhängigkeit der Magenentleerung vom Allgemeinzustand des Nervensystems. *Arch. f. d. ges. Physiol.*, 1914, clix, 389–392.
Talma, S. Zur Behandlung von Magenkrankheiten. *Ztschr. f. klin. Med.*, 1884, viii, 407–417.
Talma, S. Zur Kentniss der Tympanitis. *Berl. klin. Wchnschr.*, 1886, xxiii, 369–372.
Tappeiner, F. H. von. Zur Frage der Pylorusausschaltung. Experimentelle Untersuchungen. *Beitr. z. klin. Chir.*, 1912, lxxx, 408–424.
Tappeiner, H. Vergleichende Untersuchung der Darmgase. *Ztschr. f. physiol. Chem.*, 1882, vi, 432–479.
Tappeiner, H. Die Gase des Verdauungsschlauches der Pflanzenfresser. *Ztschr. f. Biol.* 1883, xix, 228–279.

TASHIRO, S. A Chemical Sign of Life. Chicago, 1917.

TAYLOR, A. E. Digestion and Metabolism. Philadelphia, 1912.

TAYLOR, F. B. and ALVAREZ, W. C. The effect of temperature on the rhythm of excised segments from different parts of the intestine. *Am. J. Physiol.*, 1917, xliv, 344–352.

TAYLOR, F. B., TERRY, W. I. and ALVAREZ, W. C. Improvements in preoperative and postoperative care. *J. Am. M. Assn.*, 1922, lxxix, 1578–1579.

TAYLOR, N. B. and WILSON, M. J. Observations upon the contractions of the gall-bladder. *Am. J. Physiol.*, 1925, lxxiv, 172–180.

TEZNER, O. and TUROLD, M. Pharmakologische und physiologische Studien am überlebenden menschlichen Magen. *Ztschr. f. d. ges. exper. Med.*, 1921, xii, 275–287.

THEILE, P. (a) Zur Radiologie des Säuglingsmagens mit besonderer Berücksichtigung der Gestalts- und Lageveränderungen dieses Organes bei der Füllung und Entleerung. *Ztschr. f. Kinderh.*, 1917, xv, 152–212.

THEILE, P. (b) Über die Herstellung bestimmter Aciditätsweite im Säuglingsmagen und deren Einfluss auf die Magenentleerung. *Ztschr. f. Kinderh.*, 1917, xv, 318–356.

THIEDING, F. Ueber Cardiospasmus, Atonie, und "idiopathische" Dilatation der Speiseröhre. *Beitr. z. klin. Chir.*, 1921, cxxi, 237–300.

THOMAS, J. E. The action of adrenalin on the pyloric sphincter. *Proc. Soc. Exper. Biol. & Med.*, 1926, xxiii, 748–751.

THOMAS, J. E. and KUNTZ, A. (a) A study of the vago-enteric mechanism by means of nicotin. *Am. J. Physiol.*, 1926, lxxvi, 598–605.

THOMAS, J. E. and KUNTZ, A. (b) A study of gastro-intestinal motility in relation to the enteric nervous system. *Am. J. Physiol.*, 1926, lxxvi, 606–626.

THOMAS, J. E. and WHEELON, H. The nervous control of the pyloric sphincter. *J. Lab. & Clin. Med.*, 1922, vii, 375–391.

THOMSEN, E. Über die Einwirking des Zuckers auf die Verdauung. *Ztschr. f. Phys. Chemie*, 1913, lxxxiv, 425–436.

TIEGS, O. W. Studies on plain muscle. *Austral. J. Exper. Biol. & M. Sc.*, 1924, i, 131–150.

TIGERSTEDT. Handbuch der Physiologischen Methodik. Leipzig, 1911.

TOBLER, L. Über die Eiweissverdauung im Magen. *Ztschr. f. Physiol. Chemie*, 1905, xlv, 185–215.

TODD, T. W. The Clinical Anatomy of the Gastro-Intestinal Tract. Manchester, 1915.

TOLDT, C. Die Formbildung des menschlichen Blinddarmes und die Valvula coli. *Sitzungsb. d. k. Akad. d. Wissensch., Math.-Naturw. Cl.*, 1894, ciii, Abth. 3, 41–71.

TÖNNIS, W. Die Funktion der Valvula ileocoecalis. *Arch. f. d. ges. Physiol.*, 1924, cciv, 477–482.

TOURNEUX, F. et HERMANN, G. Intestin (histologie). *Dict. encycl. d. sc. méd.*, 1889, xvi, 241–249.

TRENDELENBURG, P. Eine neue Methode zur Registrierung der Darmtätigkeit. *Ztschr. f. Biol.*, 1913, lxi, 67–72.

Trendelenburg, P. (a) Physiologische und pharmakologische Versuche über die Peristaltik des Dünndarms. *Arch. f. exper. Path. u. Pharmakol.*, 1917, lxxxi, 53–129.

Trendelenburg, P. (b) Physiologische und pharmakologische Versuche über die Peristaltik des Dünndarms. *Deutsche med. Wchnschr.*, 1917, xliii, 1225–1227.

Treves, F. The value of abdominal exploration as a medical measure. *Lancet*, 1898, i, 643-644.

Treves, F. Intestinal Obstruction. New York, 1902.

Triska, W. Experimentelle Studien über Beisskraft. *Arch. f. d. ges. Physiol.*, 1924, cciv, 660–667.

Truesdale, P. E. The pylorus: observations upon its musculature. *Surg., Gynec. & Obst.*, 1915, xxi, 298–304.

Tschekunoff, J. S. Findet eine Resorption von Nahrungssubstanzen aus dem Magen statt? *Ztschr. f. physiol. Chem.*, 1913, lxxxvii, 314–325.

Uexküll, J. von. Die ersten Ursachen des Rhythmus in der Tierreiche. *Ergebn. d. Physiol.*, 1904, iii, part 2, 1–11.

Uffenheimer, A. Weitere Studien über die Durchlässisgkeit des Magendarmkanales für Bakterien. *Deutsche med. Wchnschr.*, 1906, xxxii, 1851–1854.

Usadel, W. Untersuchungen über die Gefässversorgung des Magens zum Zweck seiner plastischen Verwendbarkeit. *Arch. f. klin. Chir.*, 1925, cxxxviii, 401–427.

Veach, H. O. Studies on the innervation of smooth muscle. *Am. J. Physiol.*, 1926, lxxvi, 532–537.

Veeder, B. S., Clopton, M. B. and Mills, R. W. Gastric motility after pyloric obstruction in infancy. *Am. J. Dis. Child.*, 1922, xxiv, 404–412.

Vella, L. Nuova metodo per avere succo enterico puro e stabilirne le proprieta fisiologiche. *Bull. d. sc. med., Bologna*, 1881, vii, 441–443.

Venables, J. F. and Knott, F. A. The investigation of the duodenal contents and bile in man. *Guy's Hosp. Rep.*, 1924, lxxiv, 245–255.

Verson, E. Stricker's Manual of Histology. American Translation by Buck. New York, 1872.

Verzar, F. Über glatte Muskelzellen mit myogenem Rhythmus. *Arch. f. d. ges. Physiol.*, 1914, clviii, 419–420.

Vinson, P. P. Hysterical dysphagia. *Minn. Med.*, 1922, v, 107–108.

Vinson, P. P. Cardiospasm. *New Orleans Med. & Surg. J.*, 1926, lxxviii, 483–490.

Wade, R. B. and Royle, R. D. The operative treatment of Hirschsprung's disease: a new method. *Med. J. Australia*, 1927, xiv, 137–141.

Waldeyer, W. Die Magenstrasse. *Sitzungsber. d. k. preuss. Akad. d. Wissensch.*, 1908, xxix, 595–606.

Wassilieff, N. Wo wird der Schluckreflex ausgelöst? *Zeitschr. f. Biol.*, 1888, xxiv, 29–46.

WATERSTON, D. The effects of formalin hardening and the persistence of irritability in the muscular coats of the intestine. *J. Anat. & Physiol.*, 1910, xlv, 16–19.

WEBER, F. P. Faecal vomiting and reversed peristalsis in functional nervous (cerebral) disease: A summary of cases and conclusions. *Brain*, 1904, xxvii, 170–198.

WEIL, A. Über dem Einfluss elektrischer Reize auf Magenperistaltik und Sekretion beim Menschen. *Deutsches Archiv. f. klin. Med.*, 1913, cix, 486–497.

WEISS, S. and HATCHER, R. A. The mechanism of the vomiting induced by antimony and potassium tartrate (tartar emetic). *J. Exper. M.*, 1923, xxxvii, 97–111.

WELCH, P. B. and PLANT, O. H. A graphic study of the muscular activity of the colon, with special reference to its response to feeding. *Am. J. M. Sc.*, 1926, clxxii, 261–269.

WERNSTEDT, W. Beiträge zum Studium des Säuglings-Pylorospasmus mit besonderer Berücksichtigung der Frage von seiner Angeborenheit. *Jahrb. f. Kinderh.*, 1907, lxv, 674–719.

WHEELON, H. Observations on gastric and duodenal motility in duodenal obstruction. *J. Am. M. Assn.*, 1921, lxxvii, 1404–1406.

WHEELON, H. Duodenal motility, radiographic observations following the direct injection of barium into the human duodenum. *J. Am. M. Assn.*, 1923, lxxx, 615–620.

WHEELON, H. Symptoms associated with duodenal retention and reverse motility. *J. Am. M. Assn.*, 1926, lxxxvi, 326–330.

WHEELON, H. and THOMAS, J. E. Observations on the motility of the antrum and the relation of the rhythmic activity of the pyloric sphincter to that of the antrum. *J. Lab. & Clin. M.*, 1920, vi, 124–143.

WHEELON, H. and THOMAS, J. E. Rhythmicity of the pyloric sphincter. *Am. J. Physiol.*, 1921, liv, 460–473.

WHEELON, H. and THOMAS, J. E. Observations on the motility of the duodenum and the relation of duodenal activity to that of the pars pylorica. *Am. J. Physiol.*, 1922, lix, 72–96.

WHITAKER, L. R. The mechanism of the gall-bladder. *Am. J. Physiol.*, 1926, lxxviii, 411–436.

WHITE, F. W. Effect of stimuli from the lower bowel on the rate of emptying the stomach. *Am. J. M. Sc.*, 1918, clvi, 184–189.

WIEDEMANN, H. Experimentelle Untersuchungen zur Lehre der Verdauung und Resorption verschiedener Nahrungsprodukte bei anormalem Gallenzufluss in den Verdauungsapparat. *Beitr. z. klin. Chir.*, 1914, lxxxix, 594–598.

WILENSKY, A. O and CROHN, B. B. Studies in the physiology and pathology of the stomach after gastroenterostomy. *Am. J. M. Sc.*, 1917, cliii, 808–824.

WILKIE, D. P. D. The blood supply of the duodenum, with special reference to the supraduodenal artery. *Surg., Gynec. & Obst.*, 1911, xiii, 399–405.

WILLIAMS, H. B. and JAMES, H. Reversal of the cardiac mechanism. *Heart*, 1914, v, 109–115.

Willigen, A. M. van der. Die Abführwirkung des Schwefels. *Arch. f. d. ges. Physiol.*, 1921, clxxxvi, 173–184.

Wilson, F. N. The production of atrioventricular rhythm in man after the administration of atropin. *Arch. Int. Med.*, 1915, xvi, 989–1007.

Winkelstein, A. The motor mechanism of the gallbladder. *J. Am. M. Assn.*, 1923, lxxx, 1748–1750.

Winkelstein, A. and Aschner, P. W. The pressure factors in the biliary-duct system of the dog. *Am. J. M. Sc.*, 1924, clxviii, 812–819.

Wislocki, G. B. and O'Connor, V. J. Experimental observations upon the ureters, with especial reference to peristalsis and antiperistalsis. *Johns Hopkins Hosp. Bull.*, 1920, xxxi, 197–202.

Wolff, W. Die Bewegungen des Duodenums, nebst Bemerkungen über einzelne Bewegungsformen des Dünndarms überhaupt. Inaug. Dissertation. Giessen, 1902.

Wollstein, M. Healing of hypertrophic pyloric stenosis after the Fredet-Rammstedt operation. *Am. J. Dis. Child.*, 1922, xxiii, 511, 517.

Wood, H. C. The treatment of phthisis by sulphuretted hydrogen. *Therap. Gaz.*, 1887, xi, 217–221.

Woodworth, R. S. Studies in the contraction of smooth muscle. *Am. J. Physiol.*, 1900, iii, 26–44.

Woodyatt, H. T. and Graham, E. A. Alimentary respiration: The secretion of CO_2 by the alimentary mucosa and its relation to eructations of gas and abnormal inflation of the stomach and intestine. *Trans. Chicago M. Times*, 1912, viii, 353–359. Also *Ohio Med. J.*, 1912, viii, 407–410.

Worden, C. B., Sailer, J., Pancoast, H. K. and Davis, G. G. A clinical study of gastroptosis, with special reference to the value of the bismuth skiagraph shadow in determining the topography of the gastro-intestinal tract. *Univ. Penn. M. Bull.*, 1906, xix, 122–141.

Wulach, Die Verweildauer der verschiedenen Nahrungssubstanzen im Magen. *München. med. Wchnschr.*, 1911, lviii, 2319–2322.

Wyman, J., Jr. Neuroid transmission in ciliated epithelium. *J. General Physiol.*, 1925, vii, 545–559.

Yanase, J. Beiträge zur Physiologie der peristaltischen Bewegungen des embryonalen Darmes. *Arch. f. d. ges. Physiol.*, 1907, cxvii, 345–383.

Yerkes, R. M. Almost Human. New York, 1925.

Yllpö, A. Über Magenatmung beim Menschen. *München. med. Wchnschr.*, 1916, lxiii, 1650.

Yllpö, A. Über Magenatmung beim Menschen, *Biochem. Ztschr.*, 1917, lxxviii, 273–293.

Zaaijer. Cardiospasmus en andere slokdarmaandoeningen. *Zentralbl. f. Chir.*, 1919, xlvi, 57–59.

Zesas, D. G. Klinik und Therapie der Vagusverletzungen am Halse. *Zentralbl. f. d. Grenzgeb. d. Med. u. Chir.*, 1915, xviii, 587–634.

Zilwa, A. E. de. Some contributions to the physiology of unstriated muscle. *J. Physiol.*, 1901, xxvii, 200–223.

ZIMMERMANN, R. Experimentelle Untersuchungen über die Empfindungen in der Schlundröhre und im Magen, in der Harnröhre und in der Blase und im Enddarm. *Mitt. a. d. Grenzgeb. d. Med. u. Chir.*, 1909, xx, 445–457.

ZONDEK, B. Über Dickdarmperistaltik. Beobachtungen am experimentellen Bauchfenster. *Arch. f. Verdauungskr.*, 1920, xxvii, 18–23.

ZUNTZ. Discussion of Tacke's work in *Verhandl. d. Ver. f. innere. Med. zu Berl.;* also *Deutsche med. Wchnschr.*, 1884, x, 717–719.

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